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**Meyerhoff et al.**

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(54) **GAS DELIVERY DEVICES**

(71) Applicant: **The Regents of the University of Michigan**, Ann Arbor, MI (US)  
(72) Inventors: **Mark E. Meyerhoff**, Ann Arbor, MI (US); **Nicolai Lehnert**, Ann Arbor, MI (US); **Yu Qin**, Ann Arbor, MI (US); **Andrew Hunt**, Ann Arbor, MI (US); **Elizabeth J. Brisbois**, Orlando, FL (US); **Hang Ren**, Oxford, OH (US)

(73) Assignee: **The Regents of the University of Michigan**, Ann Arbor, MI (US)

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**A61M 16/08** (2006.01)  
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CPC ..... **A61M 16/12** (2013.01); **A61K 33/00** (2013.01); **A61M 1/1698** (2013.01); (Continued)

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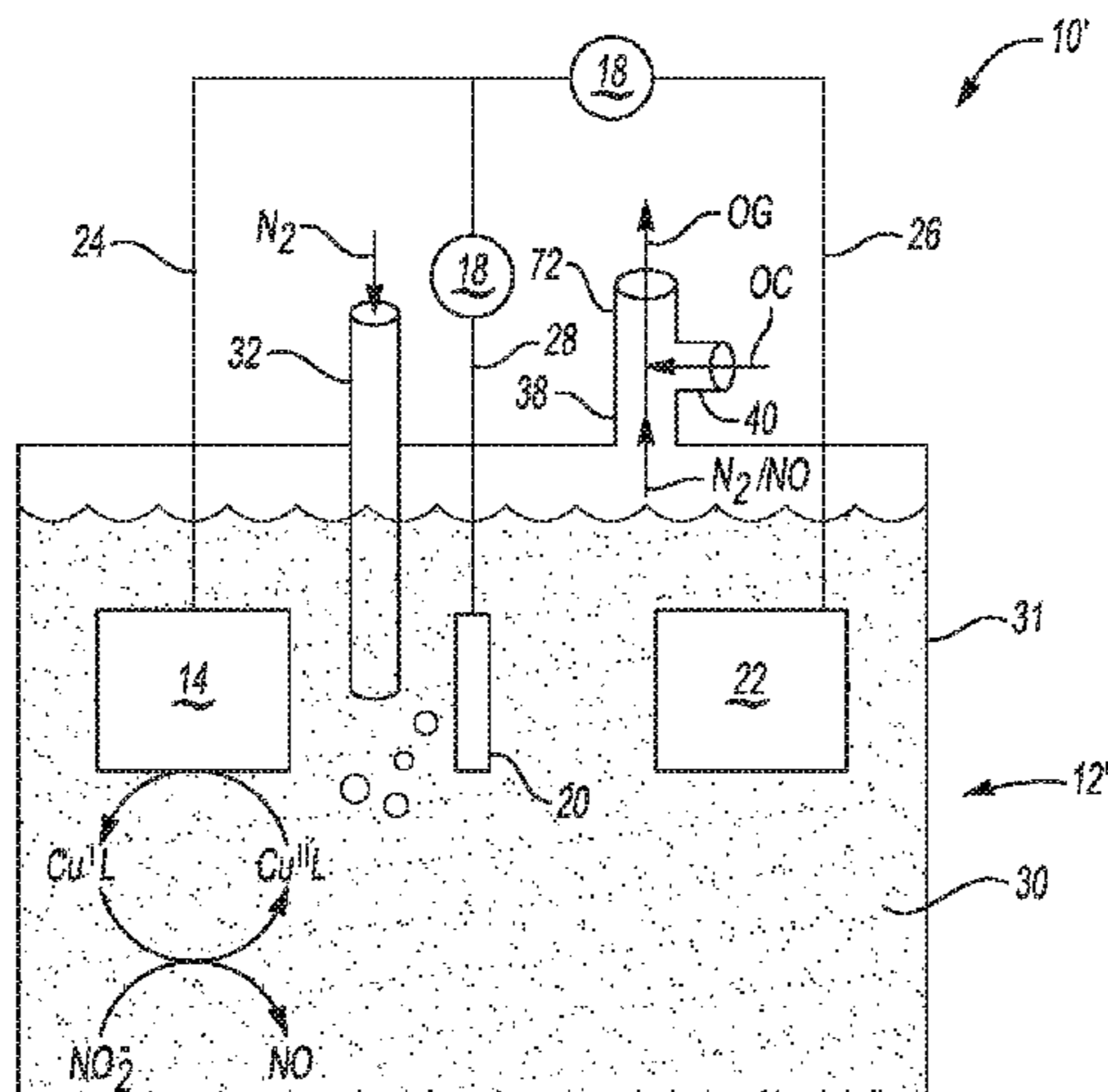
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*Primary Examiner* — Joseph D. Boecker  
(74) *Attorney, Agent, or Firm* — Dierker & Kavanaugh, P.C.

(57) **ABSTRACT**

A gas delivery device includes a nitric oxide generating system. The system has a medium including a source of nitrite ions. A working electrode is in contact with the medium. A Cu(II)-ligand complex is in contact with the working electrode. A reference/counter electrode is, or a reference electrode and a counter electrode are in contact with the medium and separated from the working electrode. An inlet conduit is to deliver nitrogen gas to the medium,  
(Continued)



and an outlet conduit is to transport a stream of nitrogen gas and nitric oxide from the medium. An inspiratory gas conduit is operatively connected to the outlet conduit to introduce an oxygen-containing gas and form an output gas stream of the gas delivery device.

**23 Claims, 13 Drawing Sheets**

**Related U.S. Application Data**

which is a continuation-in-part of application No. 15/226,769, filed on Aug. 2, 2016, now Pat. No. 10,543,337, which is a division of application No. 14/099,942, filed on Dec. 7, 2013, now Pat. No. 9,480,785, which is a continuation-in-part of application No. 13/852,841, filed on Mar. 28, 2013, now Pat. No. 9,498,571.

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See application file for complete search history.

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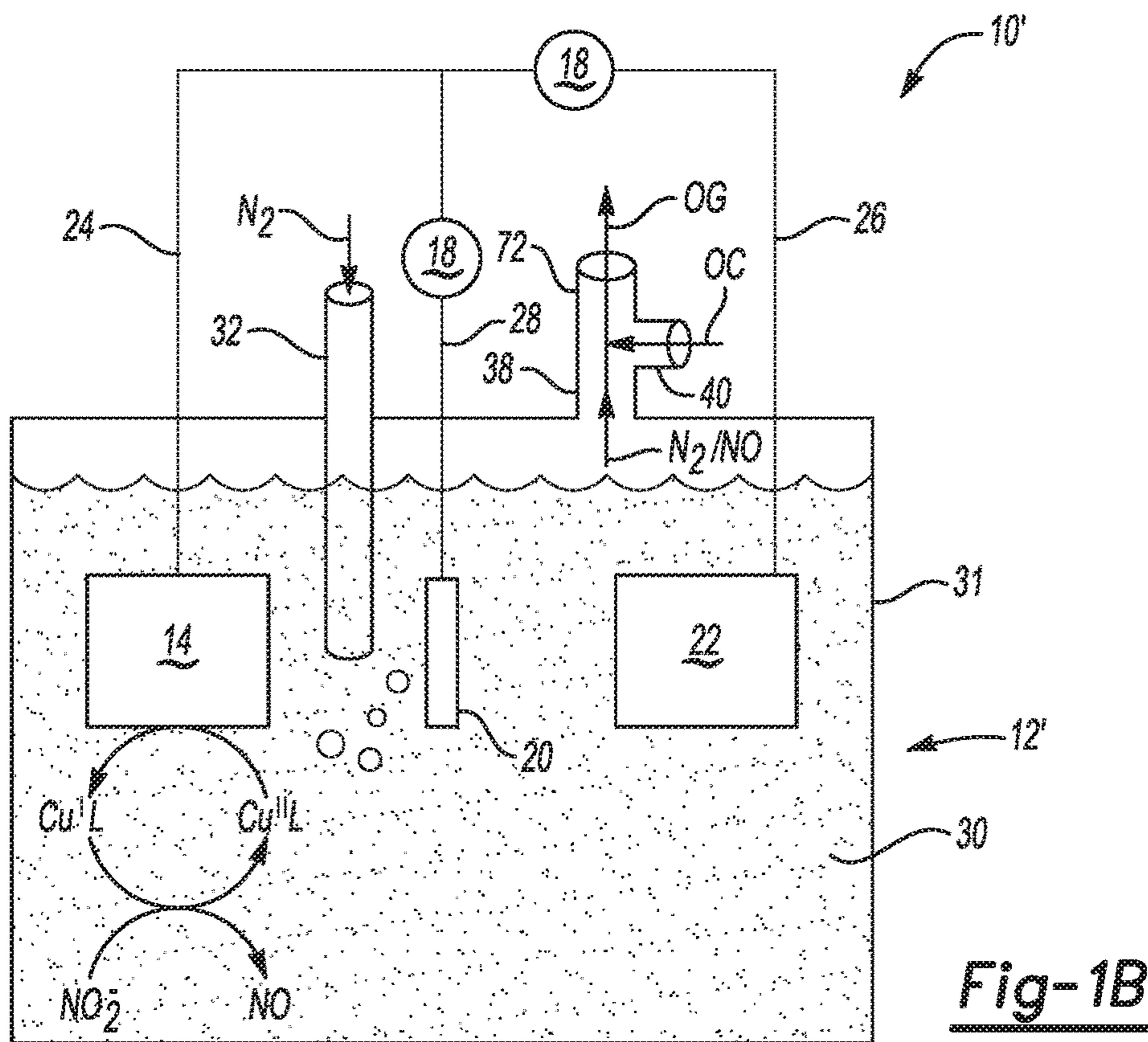
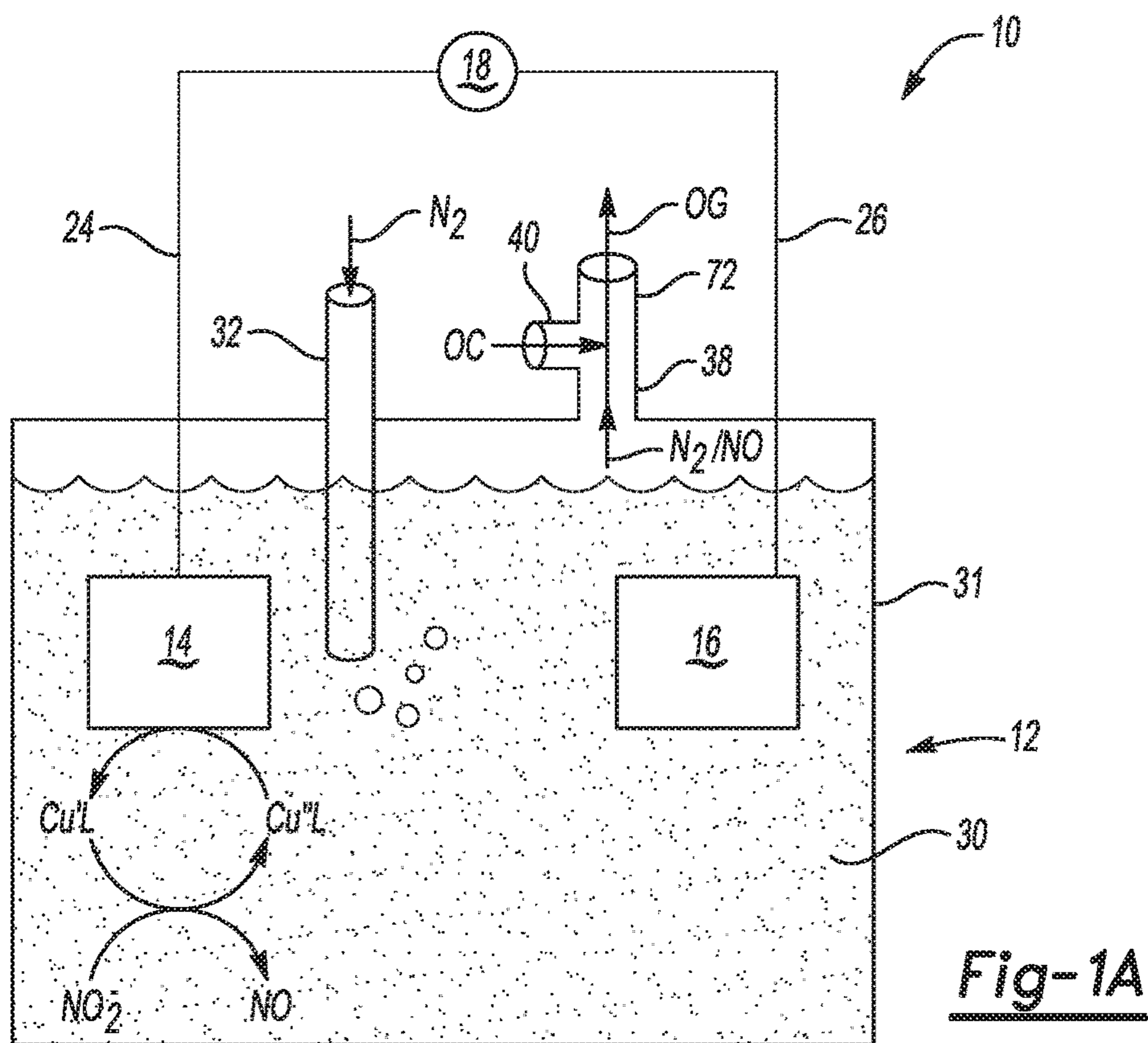
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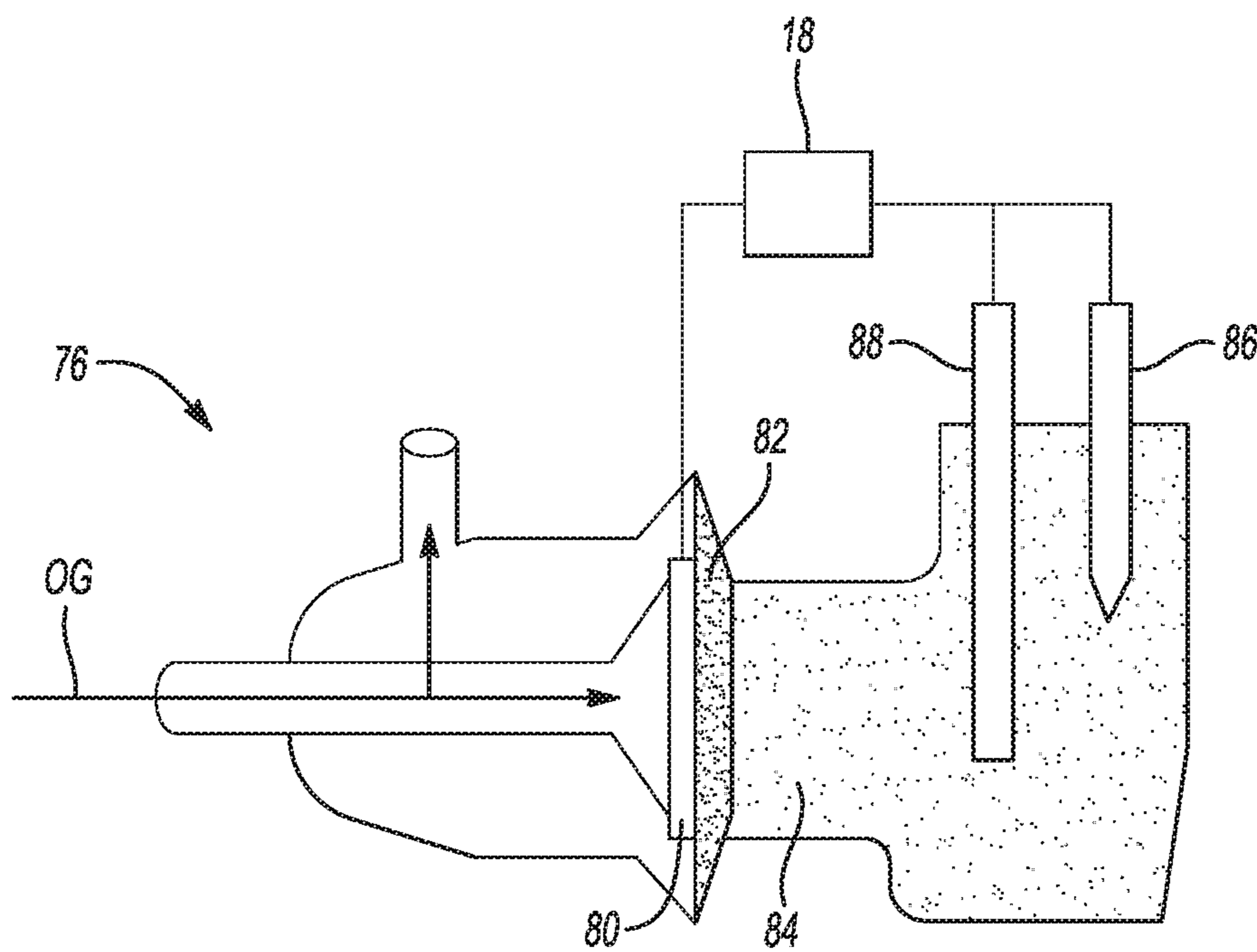
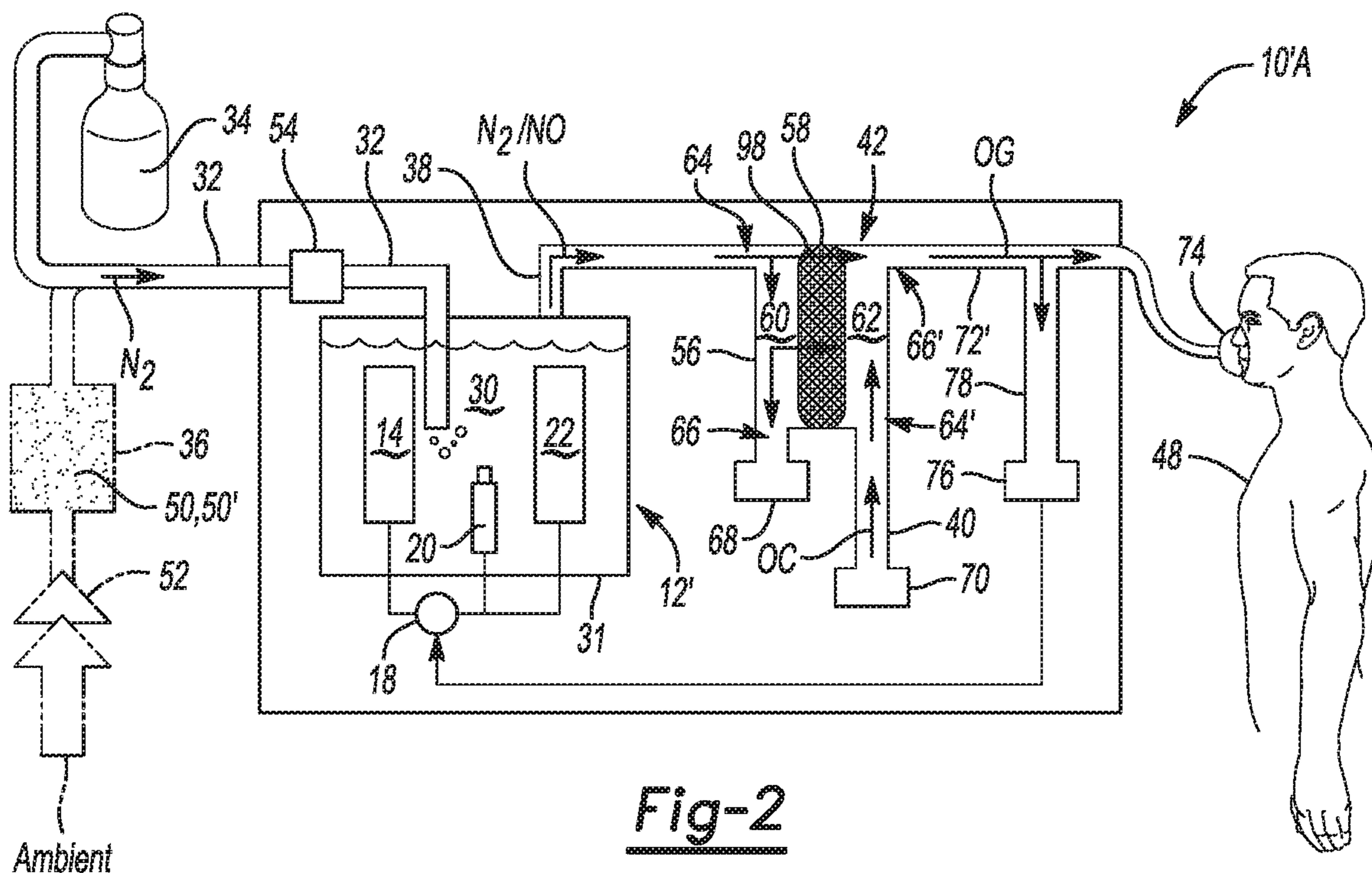
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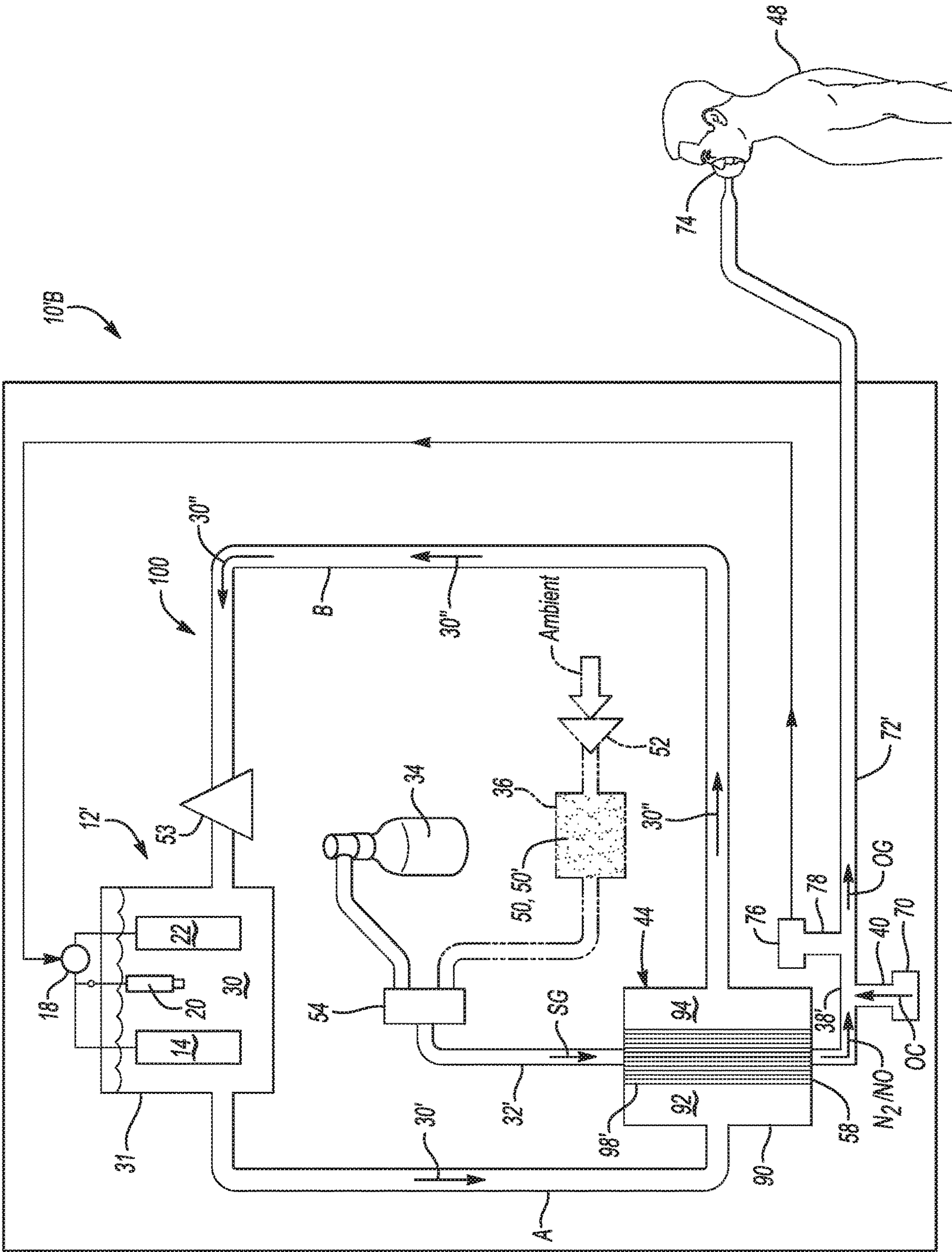


Fig-4A



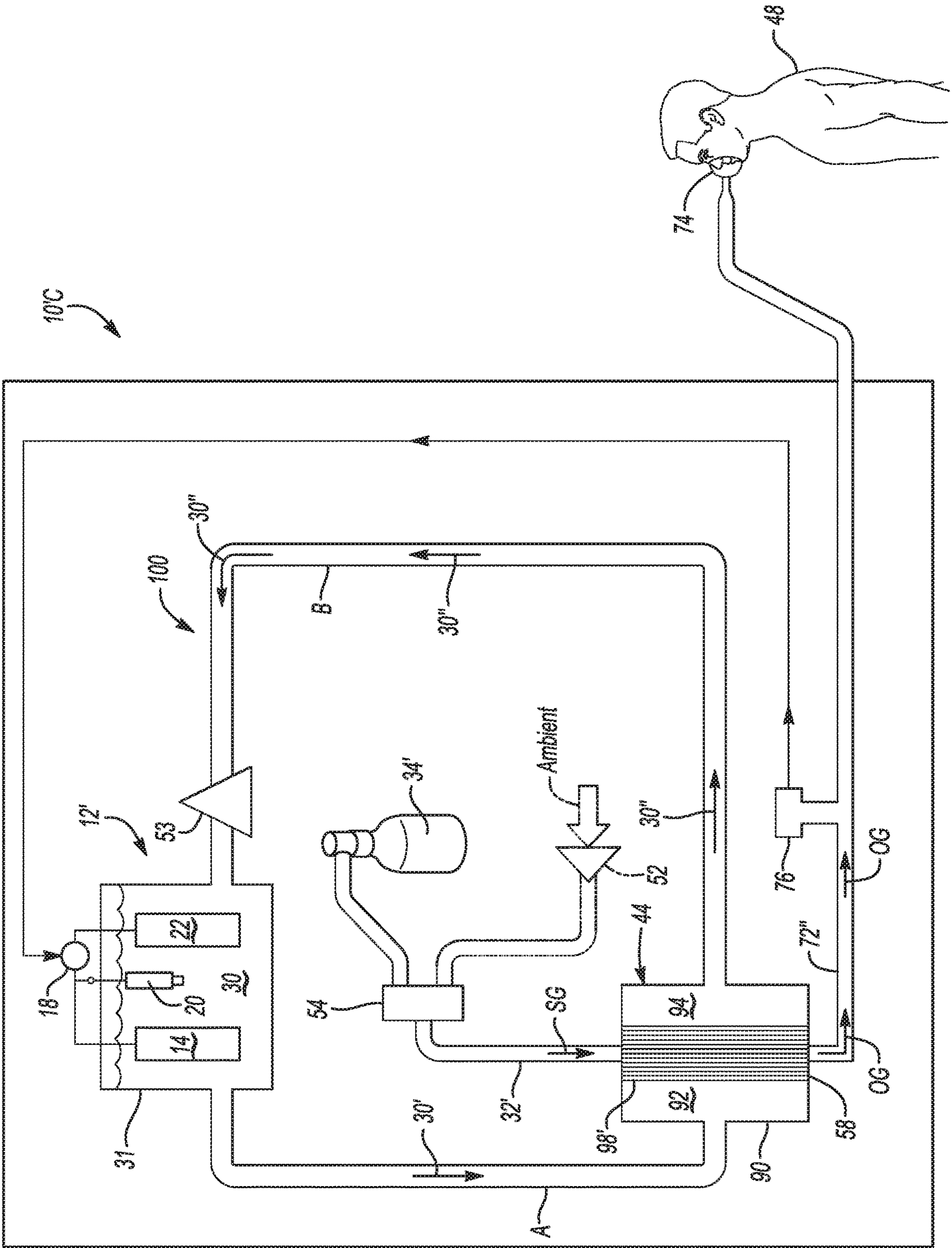


Fig-4B

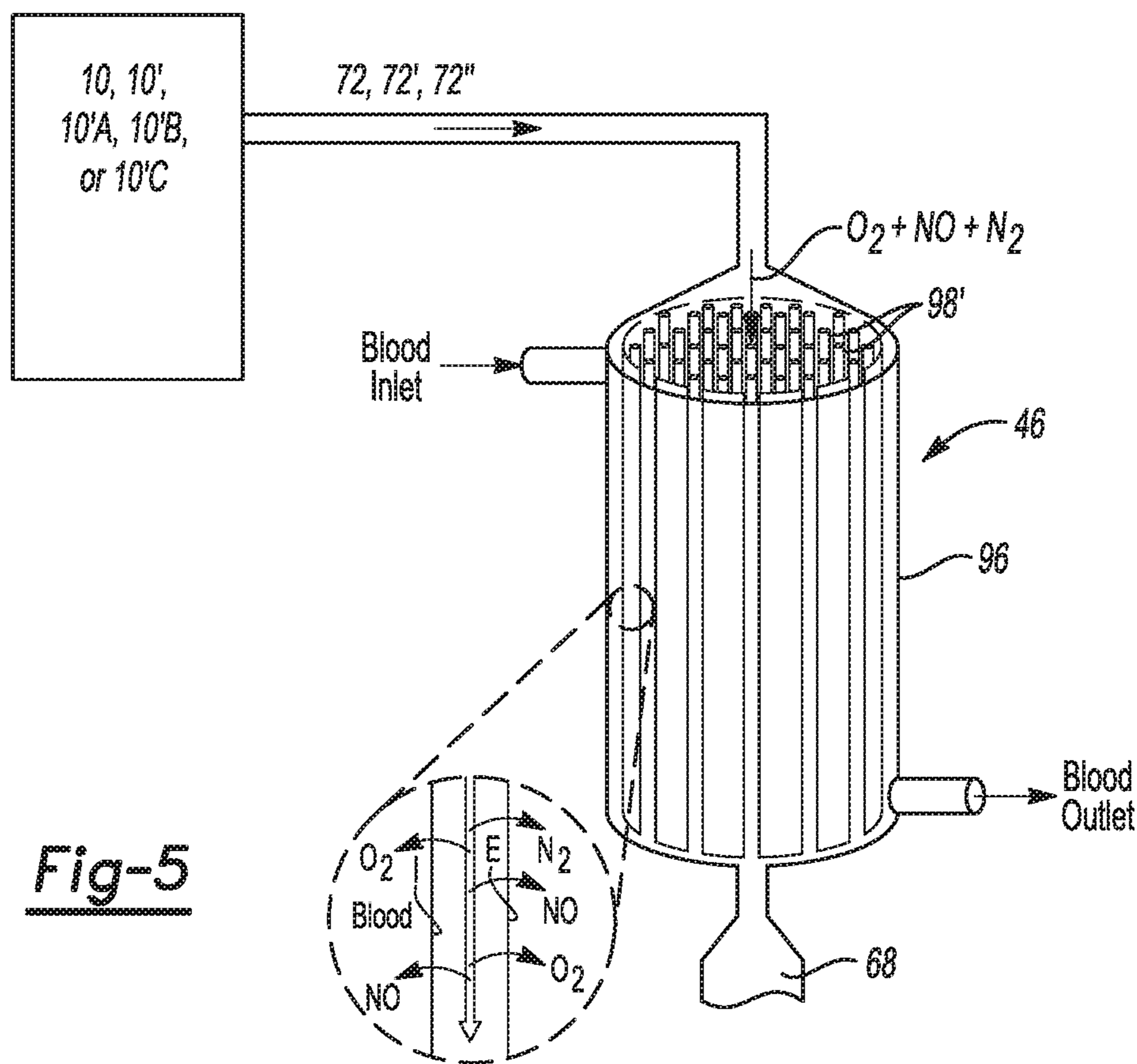


Fig-5

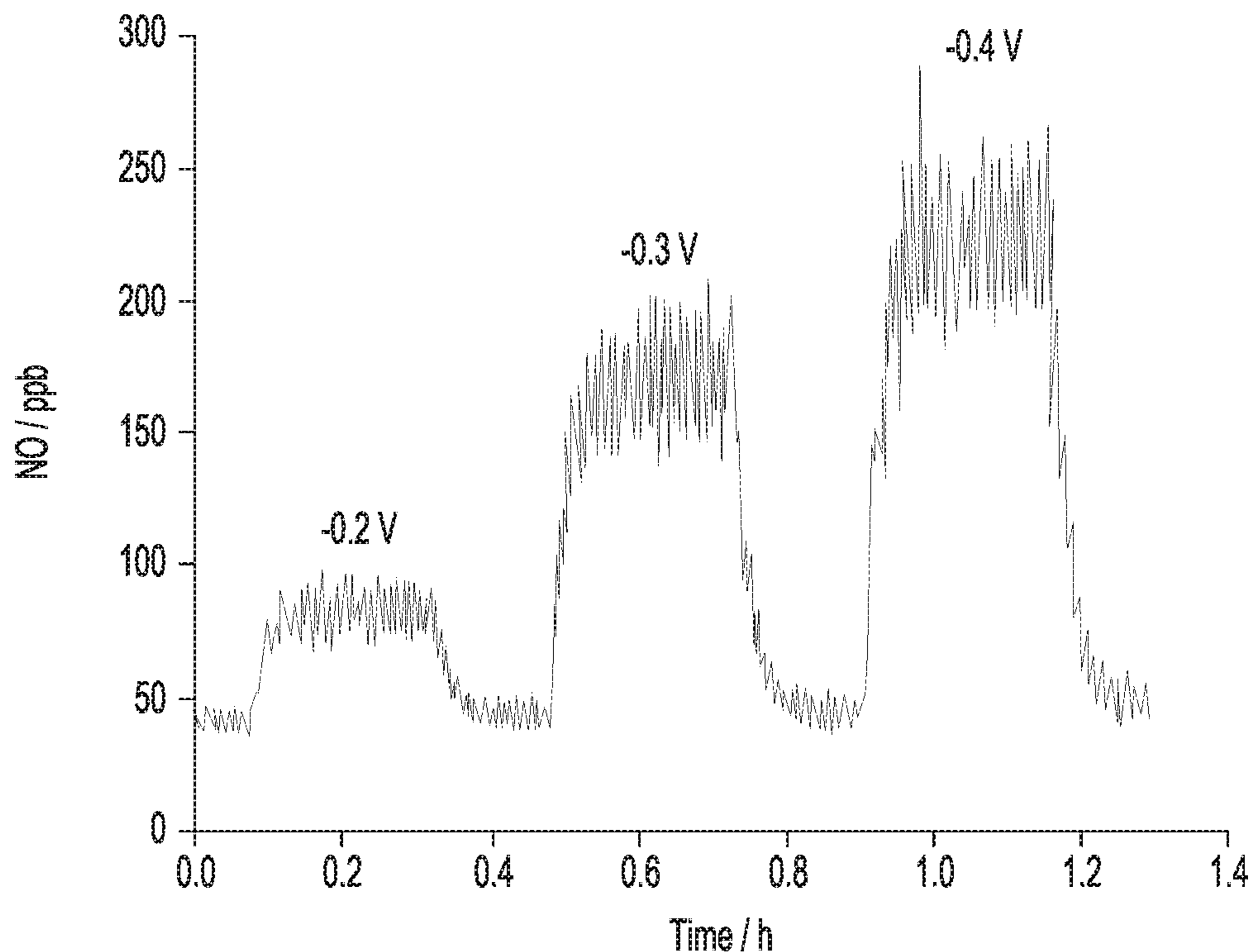


Fig-6

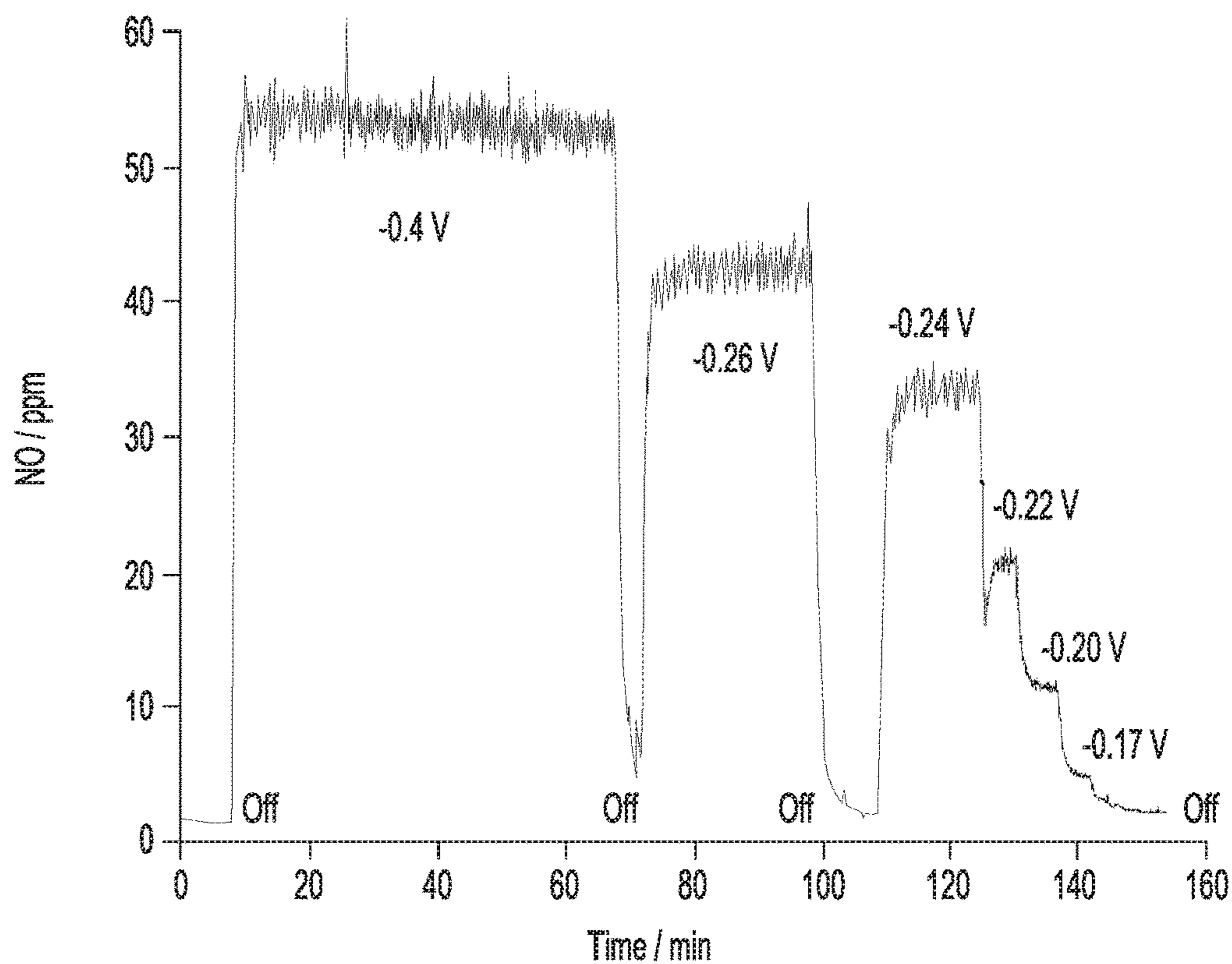


Fig-7

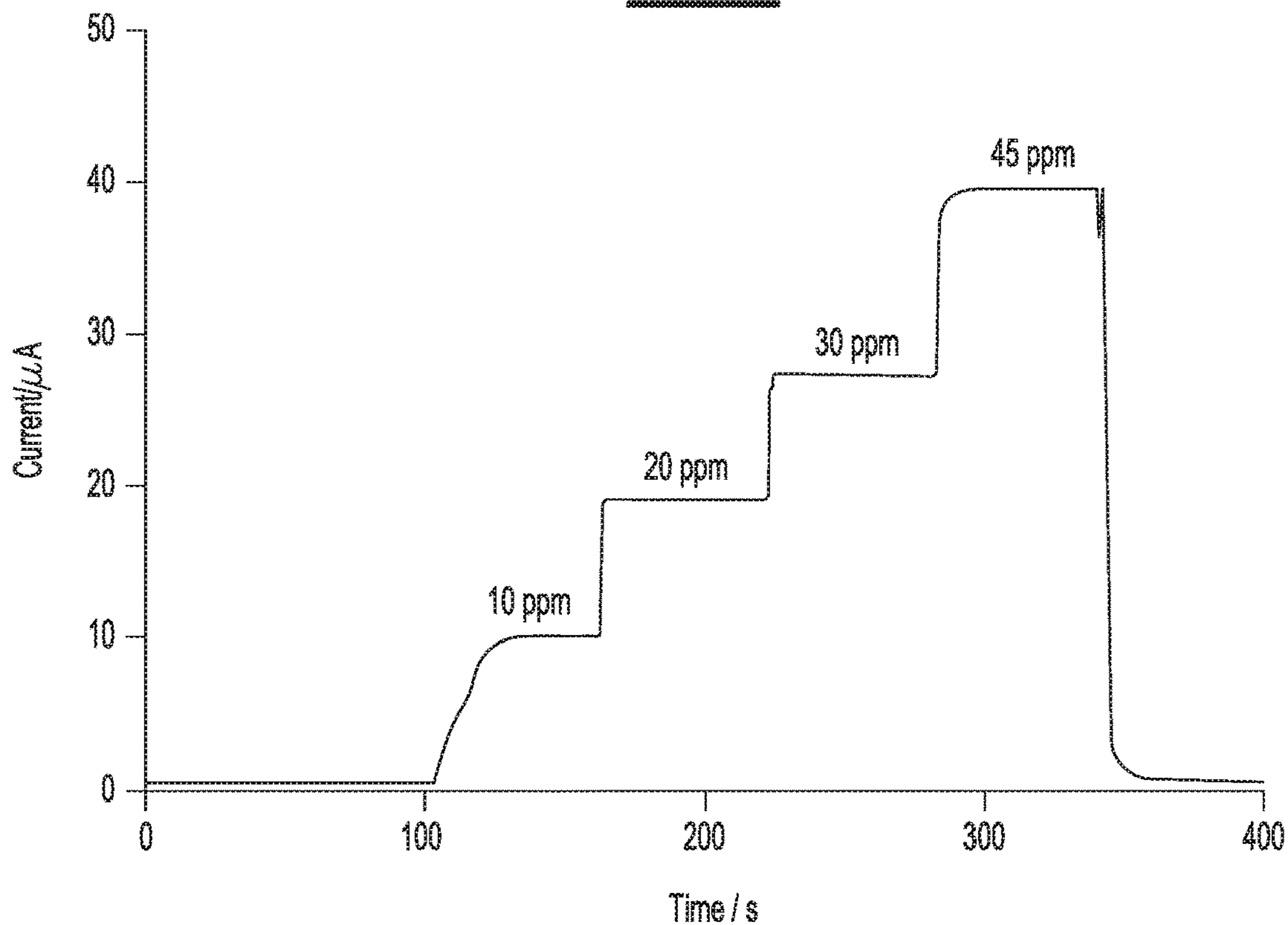
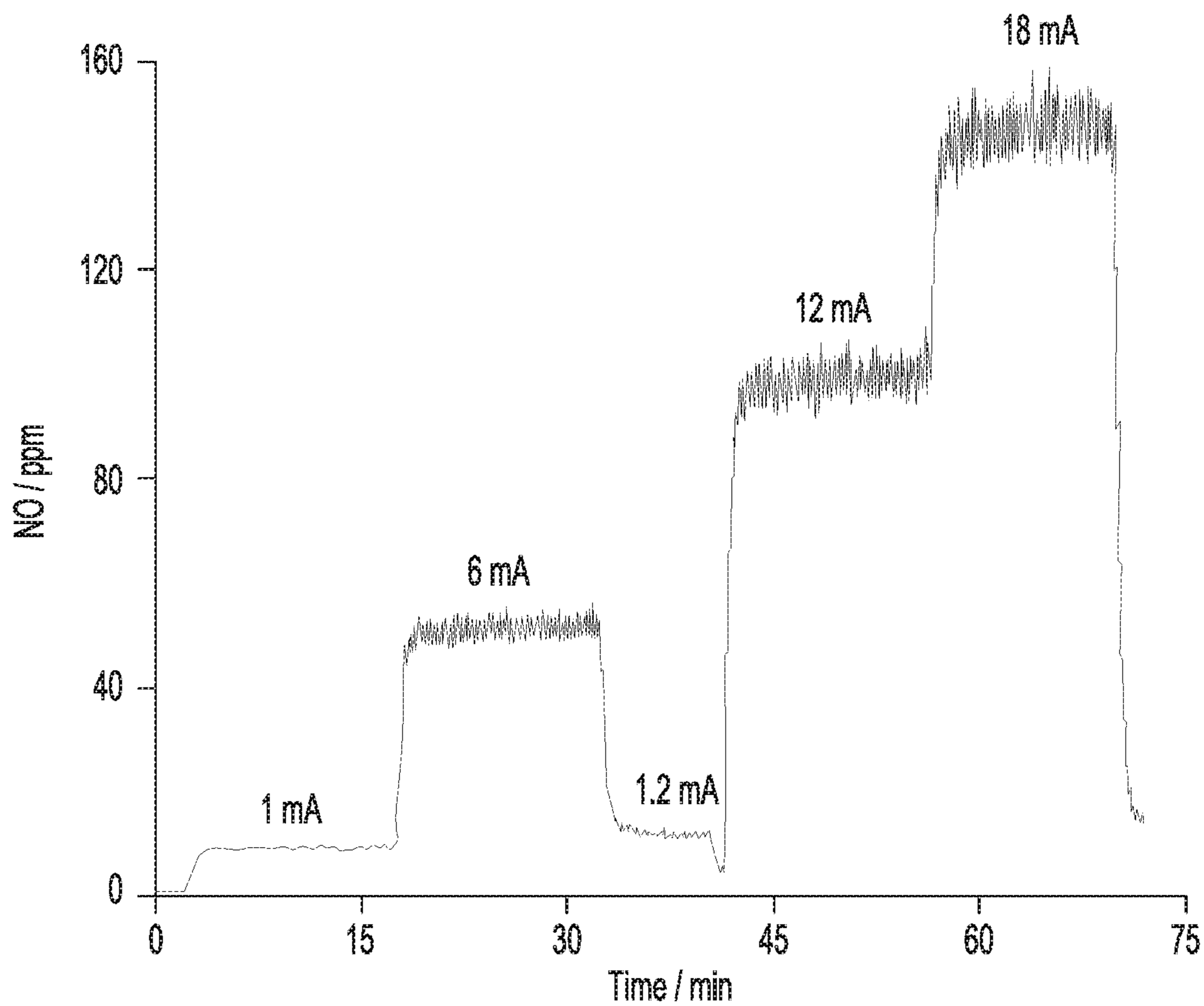
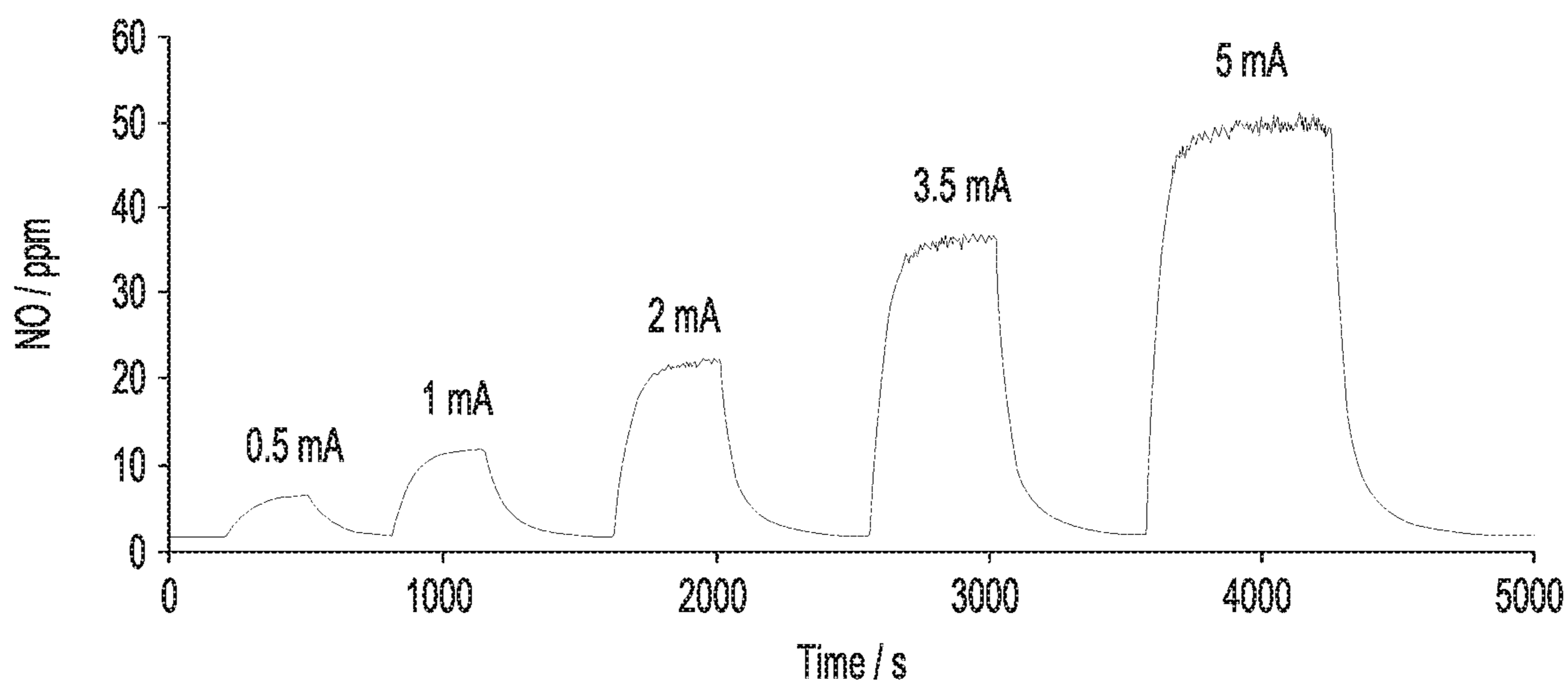


Fig-8





**Fig-9**



**Fig-10A**

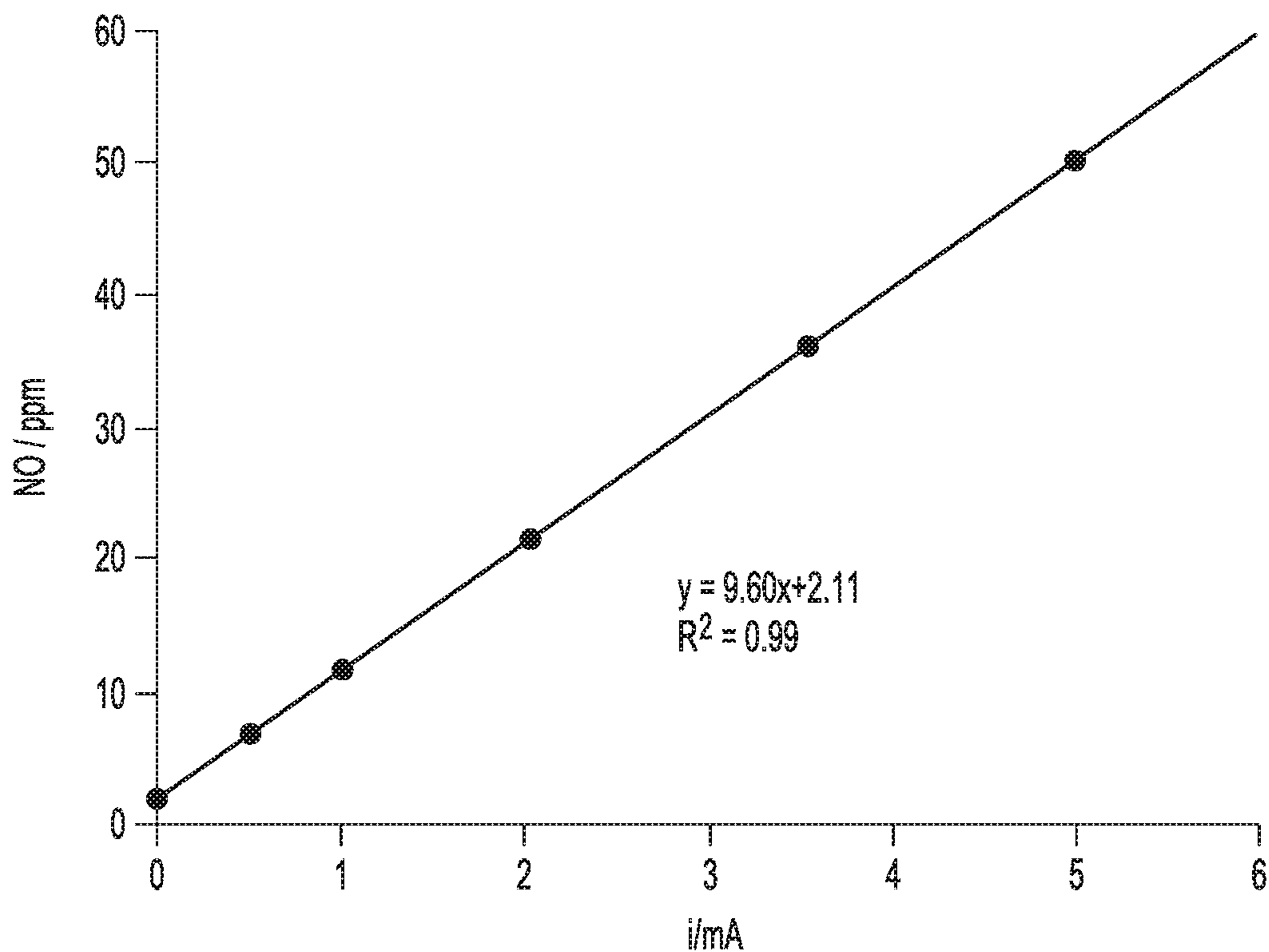


Fig-10B

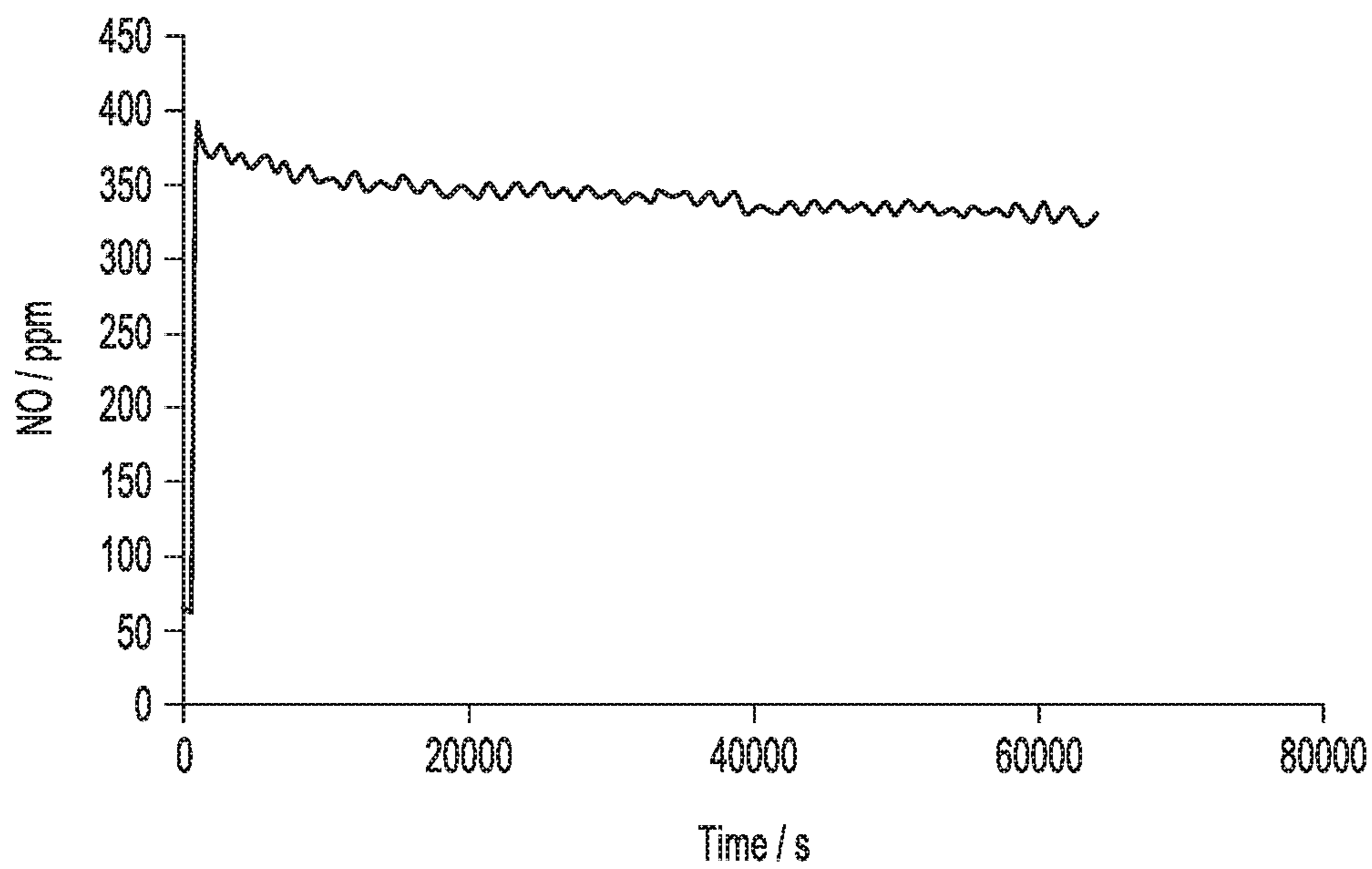


Fig-11

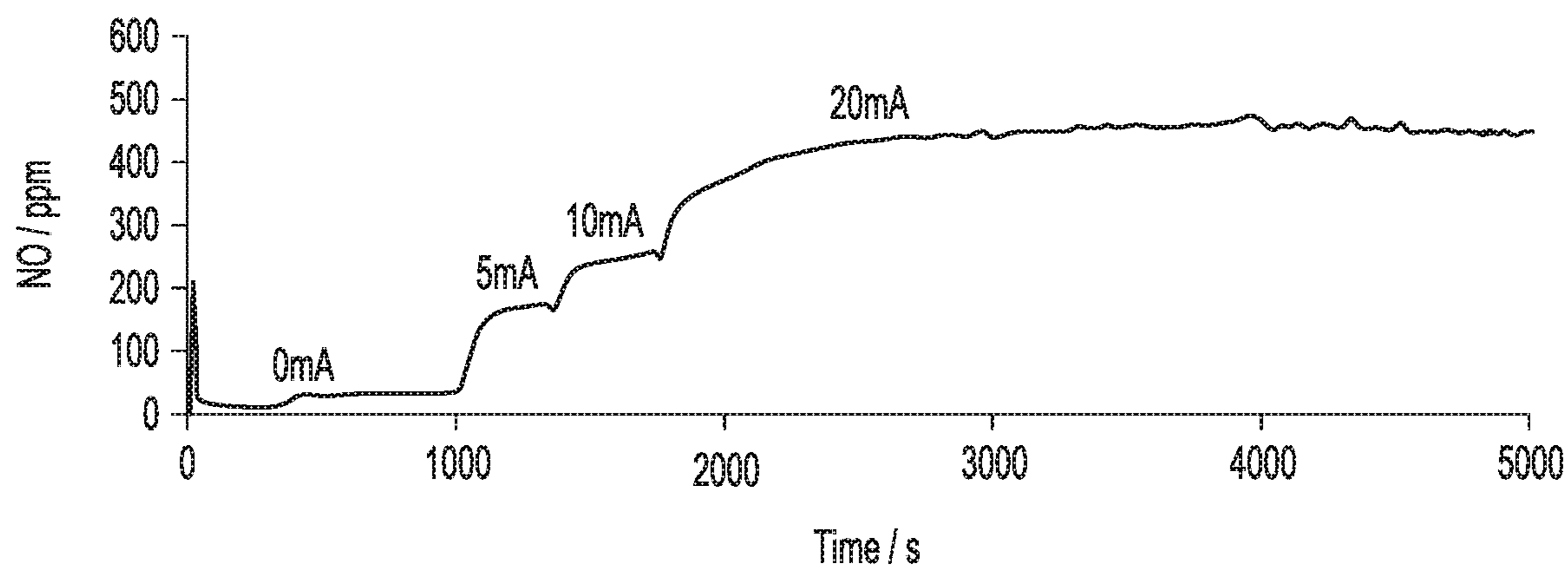


Fig-12

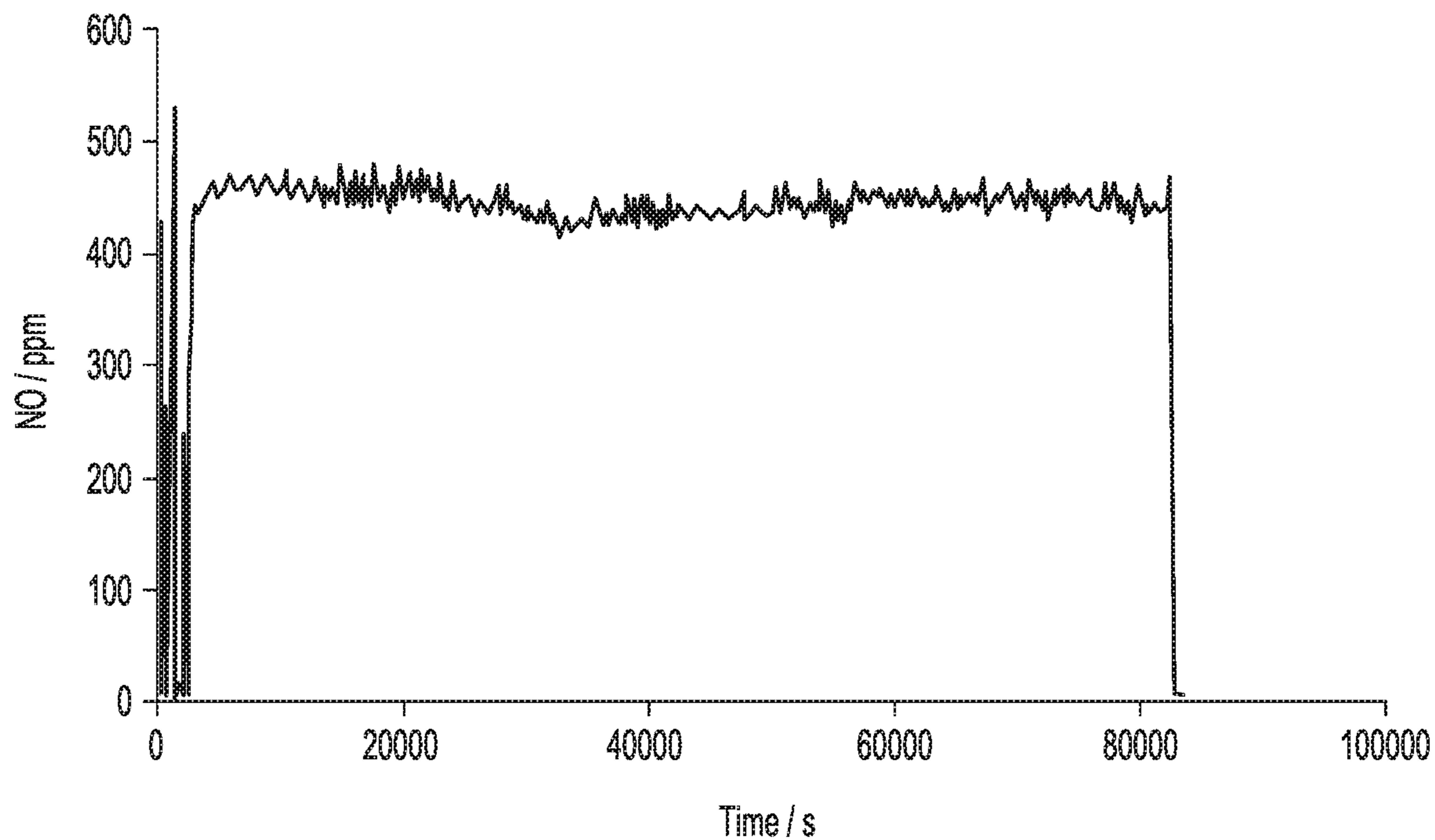


Fig-13



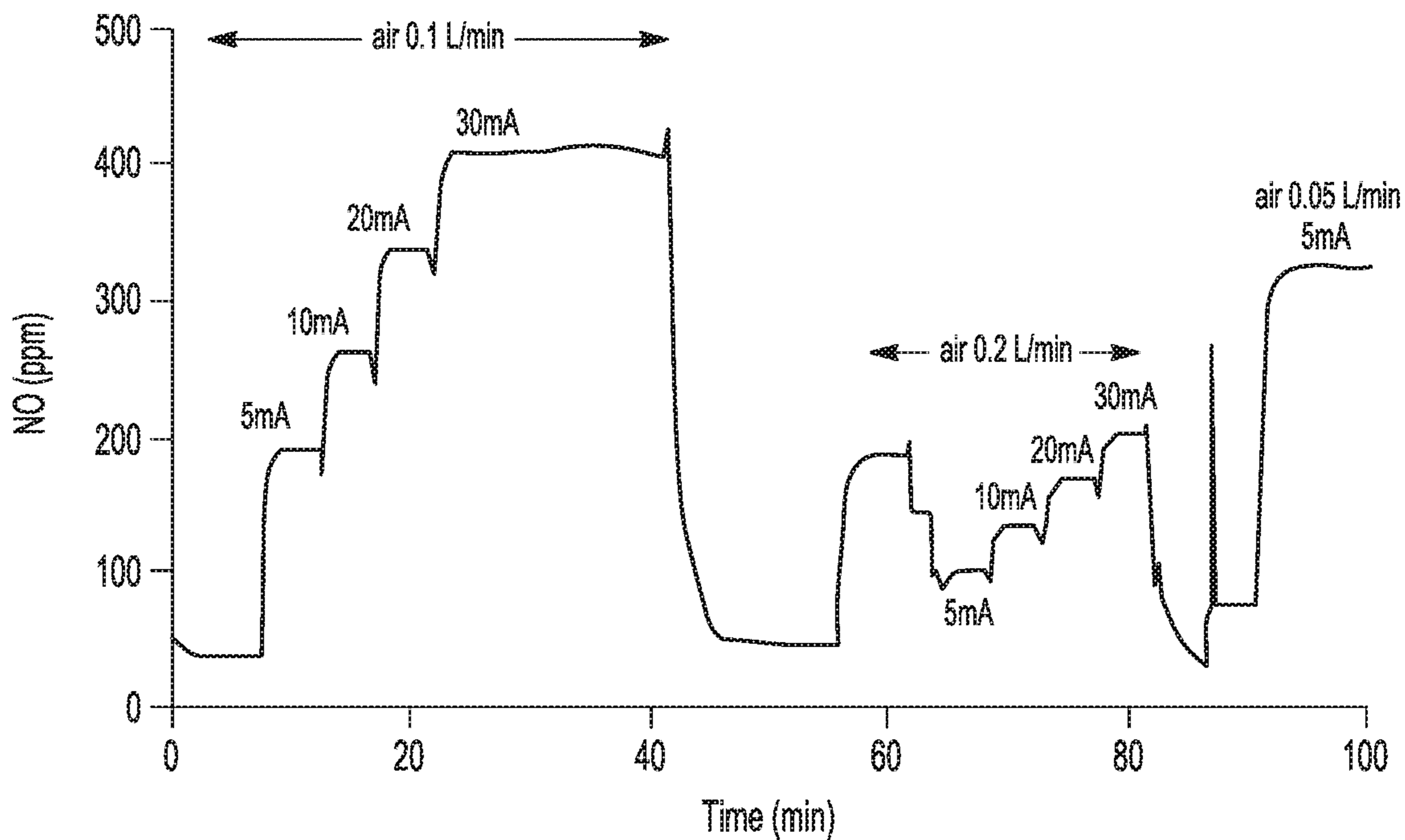


Fig-14A

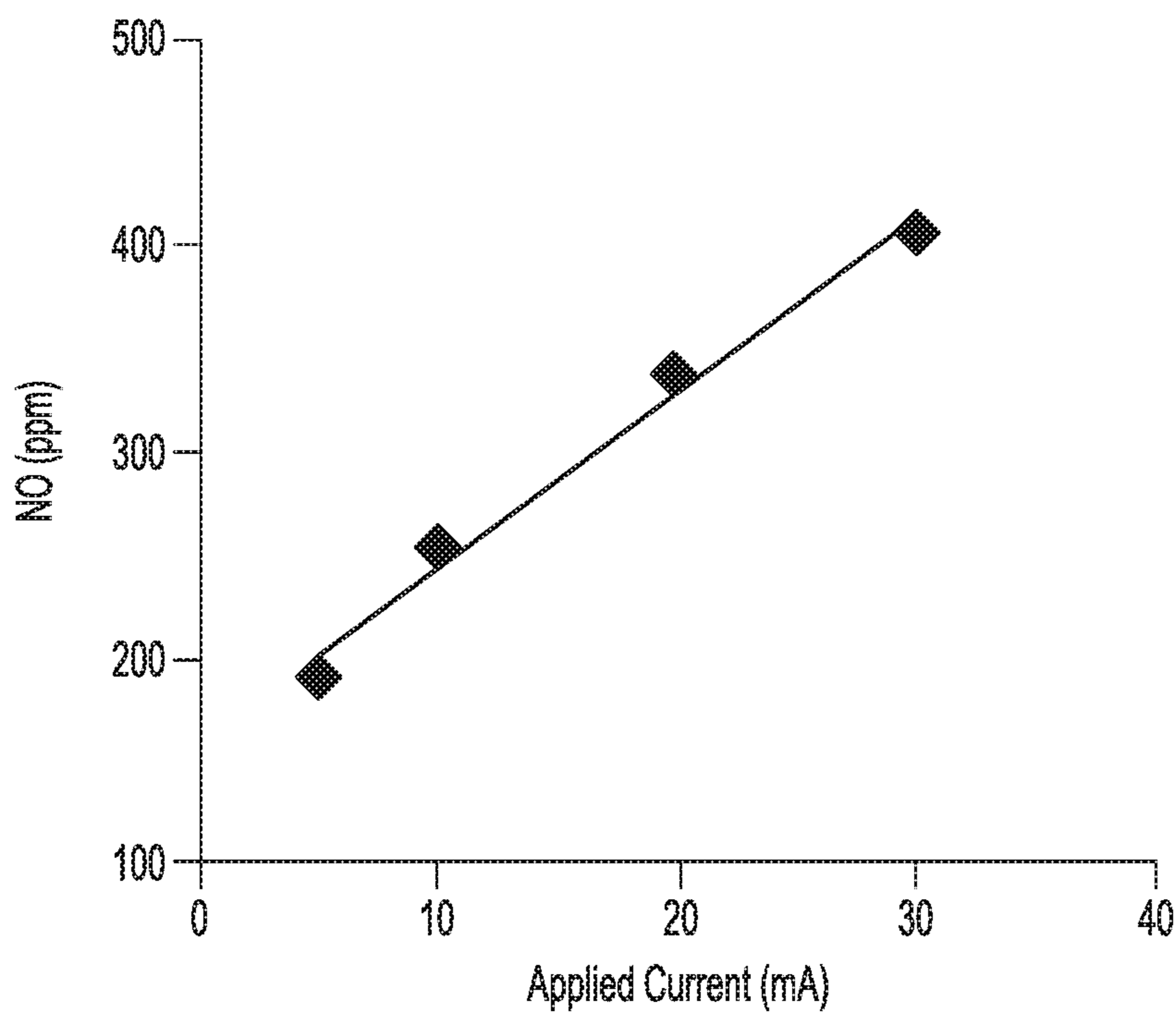
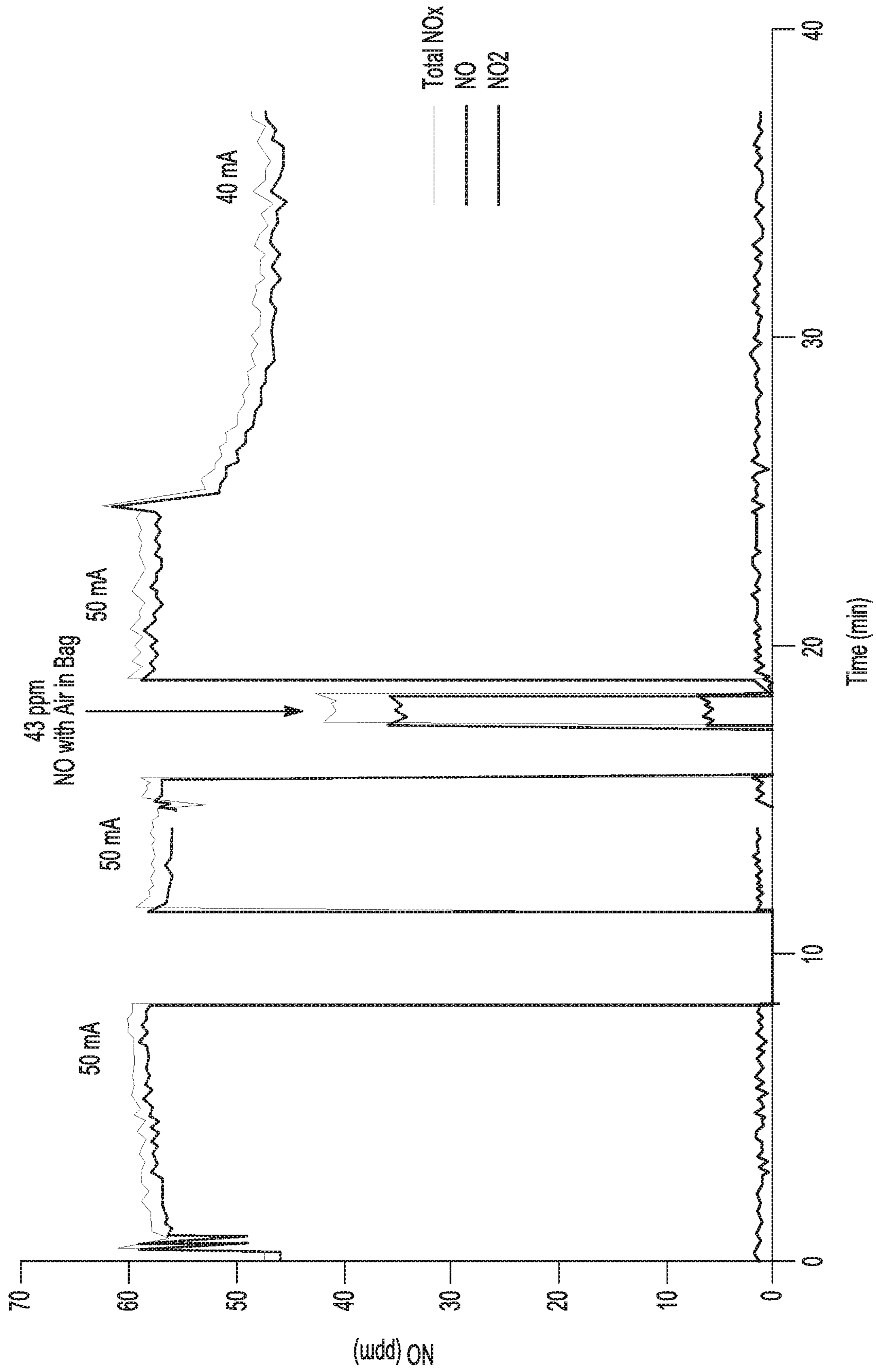


Fig-14B



**Fig-15**

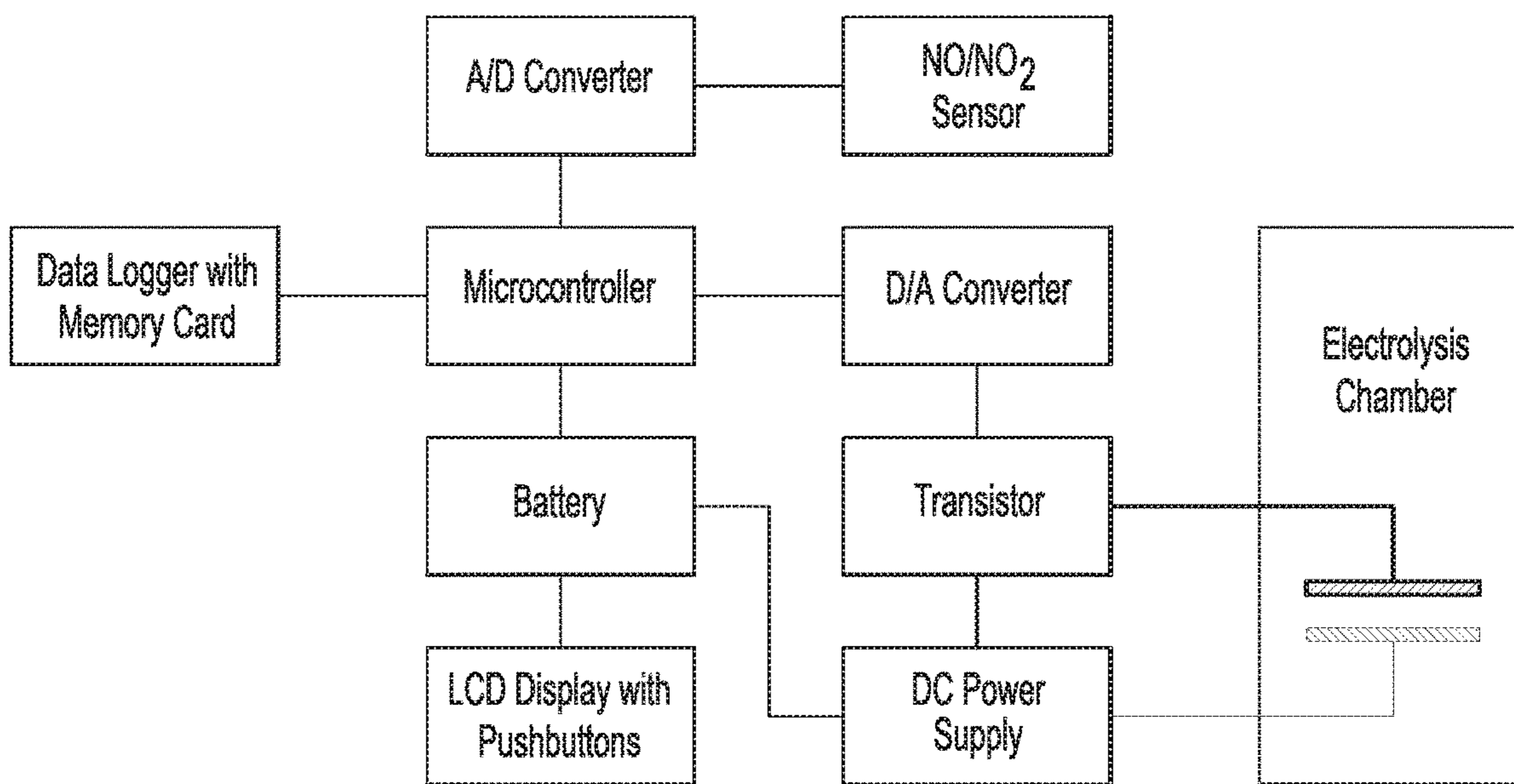


Fig-16

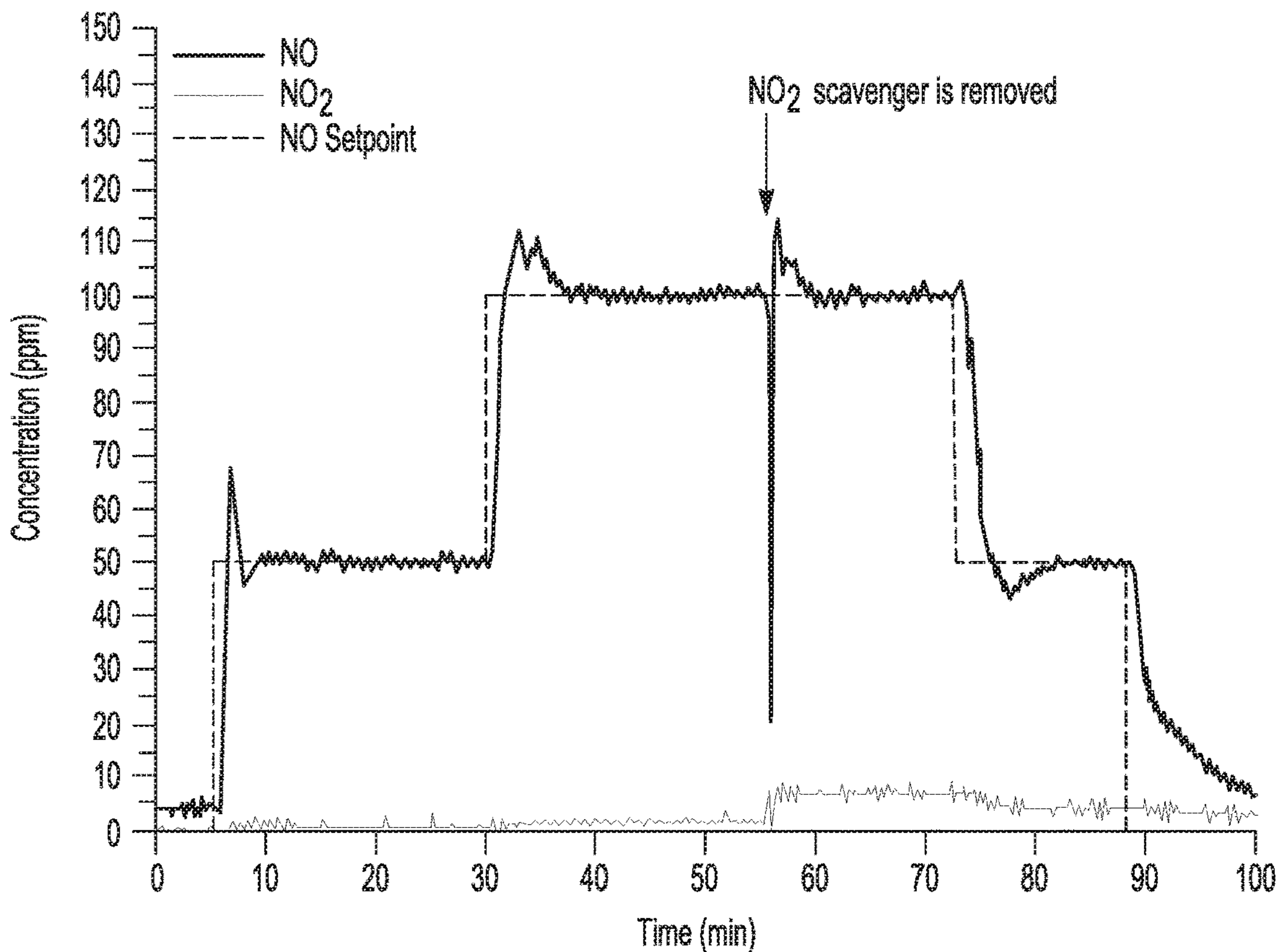
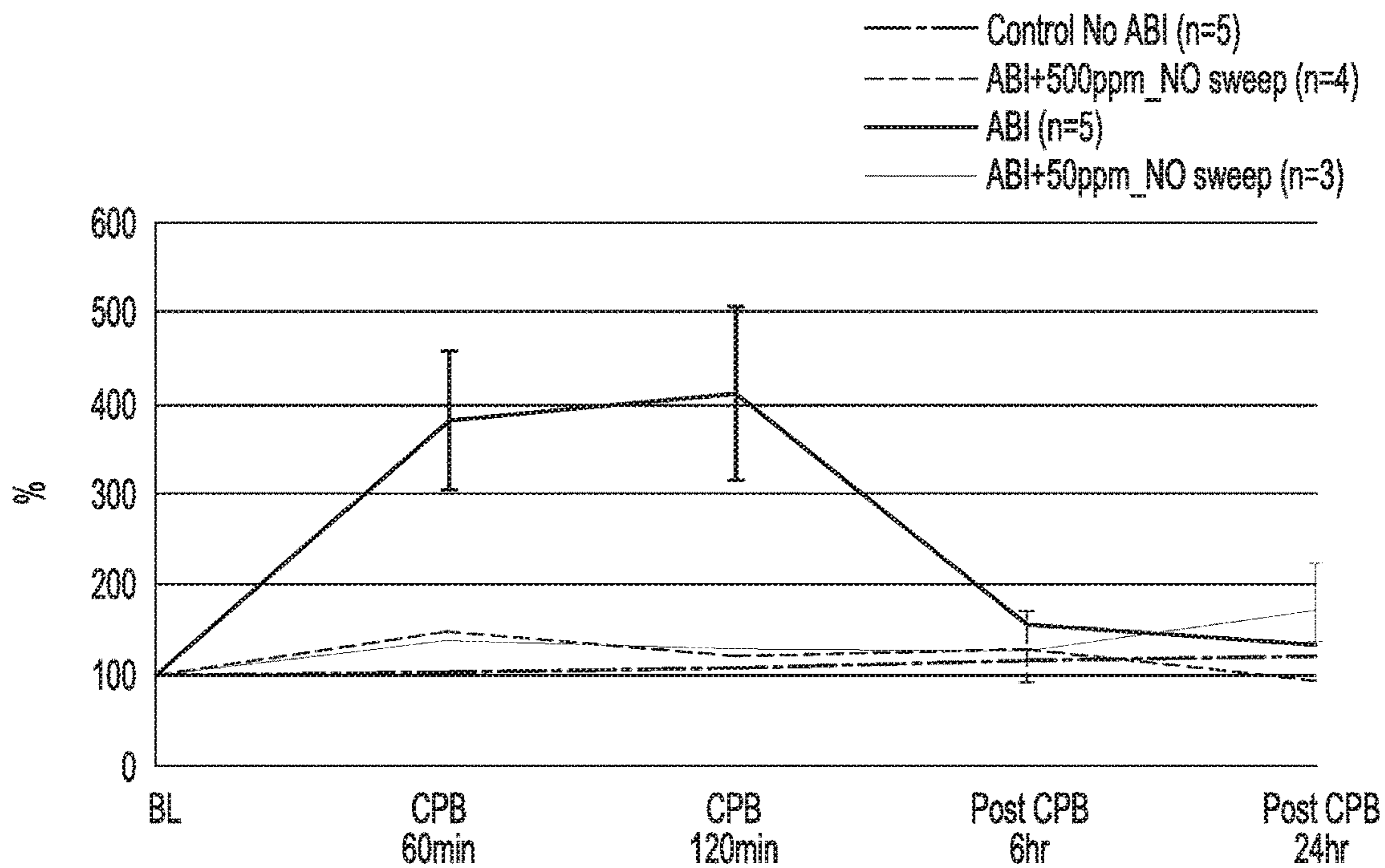


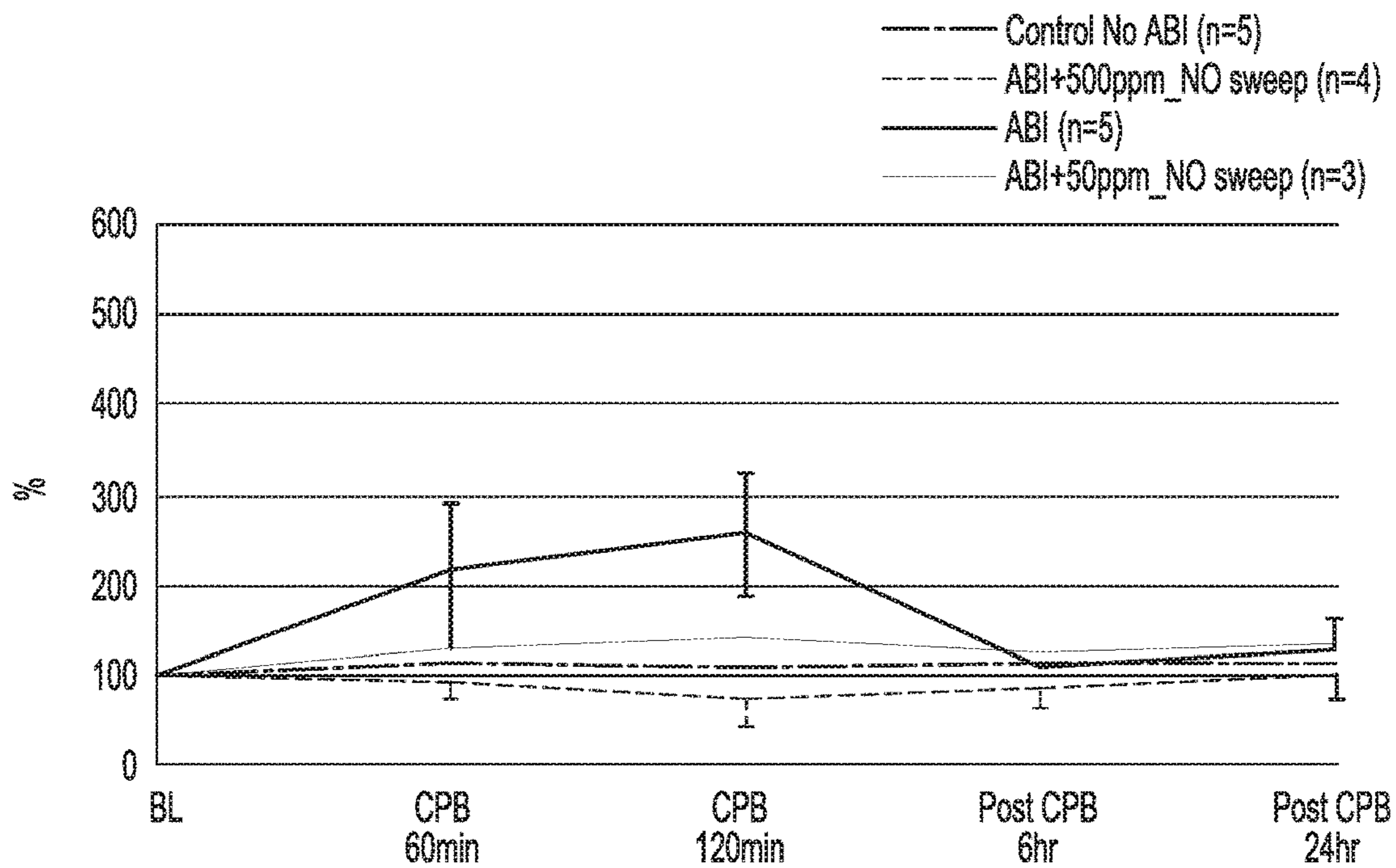
Fig-17





Experimental Time

Fig-18A



Experimental Time

Fig-18B



## 1

## GAS DELIVERY DEVICES

CROSS-REFERENCE TO RELATED  
APPLICATIONS

This application is a continuation-in-part application of U.S. Ser. No. 15/484,981, filed Apr. 11, 2017, which itself is a continuation-in-part of U.S. Ser. No. 15/226,769, filed Aug. 2, 2016, which itself is a divisional application of U.S. Ser. No. 14/099,942, filed Dec. 7, 2013 (now U.S. Pat. No. 9,480,785), which itself is a continuation-in-part application of U.S. Ser. No. 13/852,841, filed Mar. 28, 2013 (now U.S. Pat. No. 9,498,571), which itself claims the benefit of U.S. Provisional Application Ser. No. 61/617,886, filed Mar. 30, 2012, each of which is incorporated by reference herein in its entirety.

STATEMENT REGARDING FEDERALLY  
SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under Grant Nos. HD087071 and HL119403 awarded by the National Institutes of Health (NIH). The government has certain rights in the invention.

## BACKGROUND

Nitric oxide (NO) is an endogenous gas molecule that has been shown to have several important physiological functions, including its unique vasodilating properties, wound healing properties, angiogenesis promoting properties, cancer-fighting potency, anti-platelet activity, and anti-microbial/anti-viral activity. In some instances, NO can be used to control infection, prevent biofilm formation, and minimize inflammation and fibrosis.

The use of NO in inhalation therapy has also been explored. Inhaled nitric oxide has been used to treat lung failure, and has been shown to enhance pulmonary vasodilation and lower pulmonary vascular resistance. Inhaled nitric oxide has also been used to treat neonates with hypoxic respiratory failure, and has been shown to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation therapy. The use of inhaled nitric oxide may prove to be beneficial in other areas as well, such as during lung transplants, for treating pulmonary hypertension, as an inhaled antiseptic agent, etc.

## BRIEF DESCRIPTION OF THE DRAWINGS

Features of examples of the present disclosure will become apparent by reference to the following detailed description and drawings, in which like reference numerals correspond to similar, though perhaps not identical, components. For the sake of brevity, reference numerals or features having a previously described function may or may not be described in connection with other drawings in which they appear.

FIG. 1A is a schematic view of an example of a gas delivery device including a two-electrode configuration;

FIG. 1B is a schematic view of an example of the gas delivery device including a three-electrode configuration;

FIG. 2 is a schematic view of an example of a gas delivery device, including a nitric oxide generating system and a separator, being used for inhalation therapy;

FIG. 3 is an example of a nitric oxide sensor that is suitable for use in any examples of the gas delivery device disclosed herein;

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FIG. 4A is a schematic view of another example of a gas delivery device, including a nitric oxide generating system and a nitric oxide extraction device, being used for inhalation therapy;

FIG. 4B is a schematic view of another example of a gas delivery device, including a nitric oxide generating system and a nitric oxide extraction device, being used for inhalation therapy;

FIG. 5 is a schematic view of an example of a gas delivery device operatively connected to a blood oxygenator;

FIG. 6 is a graph depicting the modulation of nitric oxide generation, in terms of the NO ppb level versus time (in hours), in a bulk aqueous solution of 2 mM Cu(II)-tri(2-pyridylmethyl)amine (CuTPMA), 100 mM sodium nitrite, and 0.1 M 3-(N-morpholino)propanesulfonic acid (MOPS) buffer by applying  $-0.2$  V,  $-0.3$  V, and  $-0.4$  V (versus a 3 M  $\text{Cl}^-$  Ag/AgCl reference electrode) on a  $0.071$   $\text{cm}^2$  glassy carbon electrode;

FIG. 7 is a graph depicting the modulation of nitric oxide generation, in terms of the NO ppm level versus time (in minutes), in a bulk aqueous solution of 2 mM CuTPMA, 400 mM sodium nitrite, and 0.2 M 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffer (pH 7.2) by applying  $-0.4$  V,  $-0.26$  V,  $-0.24$  V,  $-0.22$  V,  $-0.20$  V, and  $-0.17$  V (versus a 3 M  $\text{Cl}^-$  Ag/AgCl reference electrode) on a gold mesh electrode of about  $15$   $\text{cm}^2$ ;

FIG. 8 is a graph depicting the amperometric gas phase responses, in terms of current ( $\mu\text{A}$ ) versus time (in seconds), of an example sensor disclosed herein to  $\text{NO}_{(g)}$  levels generated and swept in a nitrogen gas stream;

FIG. 9 is a graph depicting the modulation of nitric oxide generation, in terms of the NO ppm level versus time (in minutes), in a bulk aqueous solution of 7 mM Cu(II)-1,4,7-trimethyl-1,4,7-triazacyclononane ( $\text{CuMe}_3\text{TACN}$ ), 1 M sodium nitrite, and 0.5 M HEPES buffer (pH 7.3) using a constant current method on a  $25$   $\text{cm}^2$  platinum mesh electrode;

FIG. 10A is a graph depicting the modulation of nitric oxide generation, in terms of the NO ppm level versus time (in seconds), in an output gas stream containing 20% oxygen, where the NO was generated from a bulk aqueous solution of 7 mM  $\text{CuMe}_3\text{TACN}$ , 1 M sodium nitrite, and 0.5 M HEPES buffer (pH 7.3) using a constant current method on a  $25$   $\text{cm}^2$  platinum mesh electrode;

FIG. 10B is a graph depicting the NO generation of FIG. 10A in terms of NO ppm level versus the applied current (mA);

FIG. 11 is a graph depicting the modulation of nitric oxide generation, in terms of the NO ppm level versus time (in seconds), in an output gas stream including NO swept from solution by an air sweep gas at a constant flow rate of 0.05 L/min, where the NO was generated from a bulk aqueous solution of 7 mM  $\text{CuMe}_3\text{TACN}$ , 1 M sodium nitrite, and 0.5 M HEPES buffer (pH 7.3), using a constant current method on a  $4.5$   $\text{cm} \times 8.5$   $\text{cm}$  gold mesh electrode;

FIG. 12 is a graph depicting the modulation of nitric oxide generation, in terms of the NO ppm level versus time (in seconds), in an output gas stream including NO swept from solution by an oxygen sweep gas at a constant flow rate of 0.05 L/min, where the NO was generated from a bulk aqueous solution of 7 mM  $\text{CuMe}_3\text{TACN}$ , 1 M sodium nitrite, and 0.5 M HEPES buffer (pH 7.3), using a constant current method on a  $4.5 \times 4.5$   $\text{cm}^2$  stainless steel electrode;

FIG. 13 is a graph depicting the modulation of nitric oxide generation, in terms of the NO ppm level versus time (in seconds), in an output gas stream including NO swept from solution by an oxygen sweep gas at a constant flow rate of



0.05 L/min, where the NO was generated from a bulk aqueous solution of 7 mM CuMe<sub>3</sub>TACN, 1 M sodium nitrite, and 0.5 M HEPES buffer (pH 7.3), using a constant current method on a 4.5×4.5 cm<sup>2</sup> stainless steel electrode;

FIG. 14A is a graph depicting the modulation of nitric oxide generation, in terms of the NO ppm level versus time (in minutes), in an output gas stream including NO swept from solution by an air sweep gas at a constant flow rate of 0.1 L/min and 0.2 L/min, where the NO was generated from a bulk aqueous solution of from 2 mM to 7 mM CuMe<sub>3</sub>TACN and from 0.1 M to 1 M sodium nitrite, using a constant current method on a 5×10 cm<sup>2</sup> gold electrode;

FIG. 14B is a graph depicting the calibration of NO (ppm) versus the applied current at the 0.1 L/min constant flow rate of air described in conjunction with FIG. 14A;

FIG. 15 is a graph depicting the purity of gas phase NO generated using an example of the gas delivery device that includes a fluid recirculation system;

FIG. 16 is a schematic illustration of electronic circuitry used for feedback control of current passed through an electrochemical cell;

FIG. 17 is a graph depicting the feedback control of NO levels using an example of the electronic circuitry shown in FIG. 16; and

FIGS. 18A and 18B are graphs depicting the effectiveness of gaseous NO to reduce systemic inflammatory response syndrome (SIRS).

#### DETAILED DESCRIPTION

Several examples of gas delivery devices are disclosed herein. In the example devices, nitric oxide (NO) gas is generated electrochemically on demand from a solution reservoir containing a copper(II) ligand complex (i.e., Cu(II)-ligand complex) and a dissolved source of nitrite. The devices disclosed herein eliminate the need for nitric oxide tanks (i.e., NO in compressed gas cylinders), which simplifies the device and reduces the cost of the device.

Moreover, with the example gas delivery devices disclosed herein, the amount of NO that is generated may be precisely controlled by varying the voltage or current applied to a working electrode. This enables a suitable amount of NO to be generated in order to obtain a desired effect in a particular application. As one example, a steady therapeutic dose (e.g., from about 100 ppbv (parts per billion by volume) to about 100 ppmv (parts per million by volume)) of NO may be generated for inhaled nitric oxide treatments. The concentration of the NO in the output gas stream also depends, at least in part, on the flow rate of the gas(es) utilized. As another example, periodic or continuous NO generation may be used in the sweep gas of a blood oxygenator to deliver the NO to blood in order to reduce platelet activation and consumption during extracorporeal life support or cardiopulmonary bypass (CPB).

More specifically, the example gas delivery devices disclosed herein utilize a Cu(II)-ligand complex, which is in contact with the working electrode. It is to be understood that any "contact" between the Cu(II)-ligand complex and the working electrode that enables the Cu(II)-ligand complex to function as an electron mediator may be utilized. As one example, the Cu(II)-ligand complex may be in contact with the working electrode when it is dissolved or dispersed in the medium in which the working electrode is placed. As another example, the Cu(II)-ligand complex may be in contact with the working electrode by being immobilized on a surface of the working electrode. By "immobilized," it is meant that the Cu(II)-ligand complex can be covalently

attached to the working electrode, physically adsorbed to the working electrode, or doped in or covalently attached to a polymer, thin film, or hydrogel that is deposited on the working electrode surface.

These Cu(II)-ligand complexes enable one to perform an electrochemical method that uses a cathodic voltage or a cathodic current alone to generate and modulate the release of NO. In these examples, the NO is electrochemically generated by reducing the Cu(II)-ligand complex to a Cu(I)-ligand complex, the Cu(I) of which then functions to reduce nitrite ions (NO<sub>2</sub><sup>-</sup>) to NO. The NO that is generated is not bound to the reduced Cu(I) center of the ligand complex, and thus is capable of being transported out of the medium in which it is generated without performing additional steps to oxidize the ligand complex. The ratio of Cu(I)-ligand complex to Cu(II)-ligand complex at or near the surface of an inert working electrode can be controlled by controlling the applied potential or current. This enables one to control the amount of NO generated for a given concentration of nitrite and Cu(II)-ligand complex.

Any of the examples of the gas delivery device disclosed herein include a nitric oxide (NO) generating system. The NO generating system includes a medium including a source of nitrite ions; a working electrode in contact with the medium; a Cu(II)-ligand complex in contact with the working electrode; and one of: a reference/counter electrode or a reference electrode and a counter electrode in contact with the medium and separated from the working electrode. The gas delivery device further includes an inlet conduit to deliver nitrogen gas to the medium, an outlet conduit to transport a stream of nitrogen gas and nitric oxide from the medium, and an inspiratory gas conduit operatively connected to the outlet conduit to introduce an oxygen-containing gas and form an output gas stream of the gas delivery device.

Two examples of the gas delivery device **10**, **10'** and the associated NO generating system **12**, **12'** are respectively shown in FIGS. 1A and 1B. The NO generating system **12** in FIG. 1A is a two-electrode system, and the NO generating system **12'** in FIG. 1B is a three-electrode system.

In the two-electrode configuration of FIG. 1A, a working electrode **14** and a reference or counter electrode (referred to herein as a reference/counter electrode **16**) are used. In the two-electrode system, the reference and counter electrodes are shorted on the same electrode **16**. In this system, current passes through the reference/counter electrode **16**, and the potential across the complete cell can be measured. The working electrode **14** and reference/counter electrode **16** are electrically connected to a potentiostat/galvanostat **18**.

In the three-electrode configuration of FIG. 1B, the working electrode **14** is used in conjunction with a separate reference electrode **20** and a separate counter electrode **22**. In this system, current flows between the counter electrode **22** and the working electrode **14**, and the potential difference is controlled between these electrodes **22**, **14**. The potential difference is measured between the working electrode **14** and the reference electrode **20**.

In both the two-electrode and the three-electrode systems, the potentiostat/galvanostat **18** may be used to operate the circuit. The potentiostat/galvanostat **18** may include a control amplifier to force current to flow through the cell. The reference/counter electrode **16** or the counter electrode **22** may be connected to the output of the control amplifier. The potentiostat/galvanostat **18** may also include components for measuring current (e.g., a current follower for low current and/or a shunt for high current) and for measuring the potential difference (e.g., a differential amplifier).



## 5

In some of the examples disclosed herein, the potentiostat/galvanostat **18** may be switched between potentiostatic mode and galvanostatic mode.

In potentiostatic mode, the potentiostat/galvanostat **18** will accurately control the potential of the working electrode **14** so that the potential difference between the working electrode **14** and the reference electrode **20** or reference/counter electrode **16** is well defined, and corresponds to a specified value. In the examples disclosed herein, the potentiostatic mode may be used to apply a desired cathodic voltage. The application of a constant voltage can be used to produce a relatively constant level of NO.

In galvanostatic mode, the current flow between the working electrode **14** and the counter electrode **22** or the reference/counter electrode **16** is controlled. To maintain constant current, the voltage may be continuously adjusted, or adjusted as necessary. The potential difference between the working electrode **14** and the reference electrode **20** or reference/counter electrode **16** and the current flowing between the working electrode **14** and the counter electrode **22** or the reference/counter electrode **16** are continuously monitored in order to keep the current constant. For example, the cathodic voltage may be applied, and during the application of the cathodic voltage, the current at the working electrode may be monitored, and the cathodic voltage may be selectively adjusted to maintain an at least substantially constant current at the working electrode. As used herein, the "at least substantially constant current" is a current that is within +5% of a set value. In one example, the current fluctuation is less than 0.005 mA. The application of the at least substantially constant current can be used to produce the NO, and this method may result in a more constant NO level than the voltage application method. In the examples disclosed herein, the galvanostatic mode is used to apply the desired and constant cathodic current.

It is to be understood that while a potentiostat/galvanostat **18** is described, any other potential source or current source may be used for performing the examples of the method disclosed herein.

The electrical connections between the various electrodes **14**, **16**, **20**, **22** and the potentiostat/galvanostat **18** (or various components thereof) may be through conductive leads. For example, as shown in FIG. 1A, conductive leads **24** and **26** respectively and electrically connect the working electrode **14** and the reference/counter electrode **16**. More specifically, the conductive leads **24**, **26** electrically connect the respective electrodes **14**, **16** to the potentiostat/galvanostat **18** that is used to control and monitor the applied voltage or current. For another example, as shown in FIG. 1B, conductive leads **24** and **26** respectively and electrically connect the working electrode **14** and the reference/counter electrode **16**, and conductive lead **28** electrically connects the reference electrode **20** to the working and counter electrodes **14**, **22**. As illustrated, the conductive leads **24**, **26**, **28** electrically connect the respective electrodes **14**, **22**, **20** to the potentiostat/galvanostat **18** that is used to control and monitor the applied voltage or current. The conductive leads **24**, **26**, **28** may be made of any conductive material, examples of which include copper wires, platinum wires, stainless steel wires, aluminum wires, etc.

Any suitable working electrode **14** may be used. Examples of the working electrode **14** include platinum, gold, carbon (e.g., glassy carbon, carbon paste, carbon cloth, etc.) or a carbon coated material, mercury, stainless steel, a base electron conducting material having a thin film of platinum thereon, a base electron conducting material having a thin film of gold thereon, etc. Examples of the base

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electron material include platinum, gold, carbon or a carbon coated material, mercury, stainless steel, titanium, a metal coated polymer, a conductive polymer, a semiconductor (e.g., silicon, etc.), or the like. In an example, the thin film of platinum or gold may have a thickness ranging from about 2 nm to about 10  $\mu\text{m}$ . In another example, the thin film of platinum or gold may have a thickness ranging from about 10 nm to about 1  $\mu\text{m}$ . The thin may be deposited on the base electrode using any suitable vapor deposition method. As examples, platinum or gold may be deposited via chemical vapor deposition (CVD) or plasma enhanced chemical vapor deposition (PECVD) on a plastic mesh base electrode. Other suitable deposition methods, such as electroplating or sputtering may also be used.

The working electrode **14** may have a relatively large surface area since (as shown schematically in both FIGS. 1A and 1B) the reaction of the Cu(II)-ligand complex used to electrochemically generate the NO takes place at the working electrode **14**. The larger the surface area of the working electrode **14**, the more NO that will be generated at a given current density or applied voltage. As such, the surface area of the working electrode **14** can depend, at least in part, on the desired concentration of NO and the flow rate that is to be used. In an example, the surface area of the working electrode **14** ranges from about 0.1  $\text{cm}^2$  to about 200  $\text{cm}^2$ . In another example, the surface area of the working electrode **14** ranges from about 4  $\text{cm}^2$  to about 50  $\text{cm}^2$ . In still another example, the surface area of the working electrode **14** ranges from about 15  $\text{cm}^2$  to about 25  $\text{cm}^2$ .

In the two-electrode system, any suitable reference/counter electrode **16** may be used. For example, the reference/counter electrode **16** may be silver/silver chloride or some other reference electrode (e.g., mercury sulfate electrode, saturated calomel electrode) or pseudo reference electrode (e.g., gold, platinum, stainless steel, a sodium-selective electrode, a potassium-selective electrode, or the like). In an example of the three-electrode system, the reference electrode **22** is silver/silver chloride and the counter electrode **22** is platinum (e.g., a platinum mesh), gold, stainless steel, carbon (e.g., glassy carbon) or a carbon coated material, titanium, indium tin oxide (ITO), etc. In the three-electrode system, the reference electrode **22** may also be any of the previously mentioned reference electrodes or pseudo reference electrodes.

In an example, the electrodes **14**, **16**, **20**, **22** may be in the form of mesh electrodes, which may be a network of wires or screen printed lines.

In both the two- and three-electrode systems, the medium **30** used to generate the NO includes a source of nitrite ions. In some examples, the medium **30** also has the Cu(II)-ligand complex dissolved or dispersed therein.

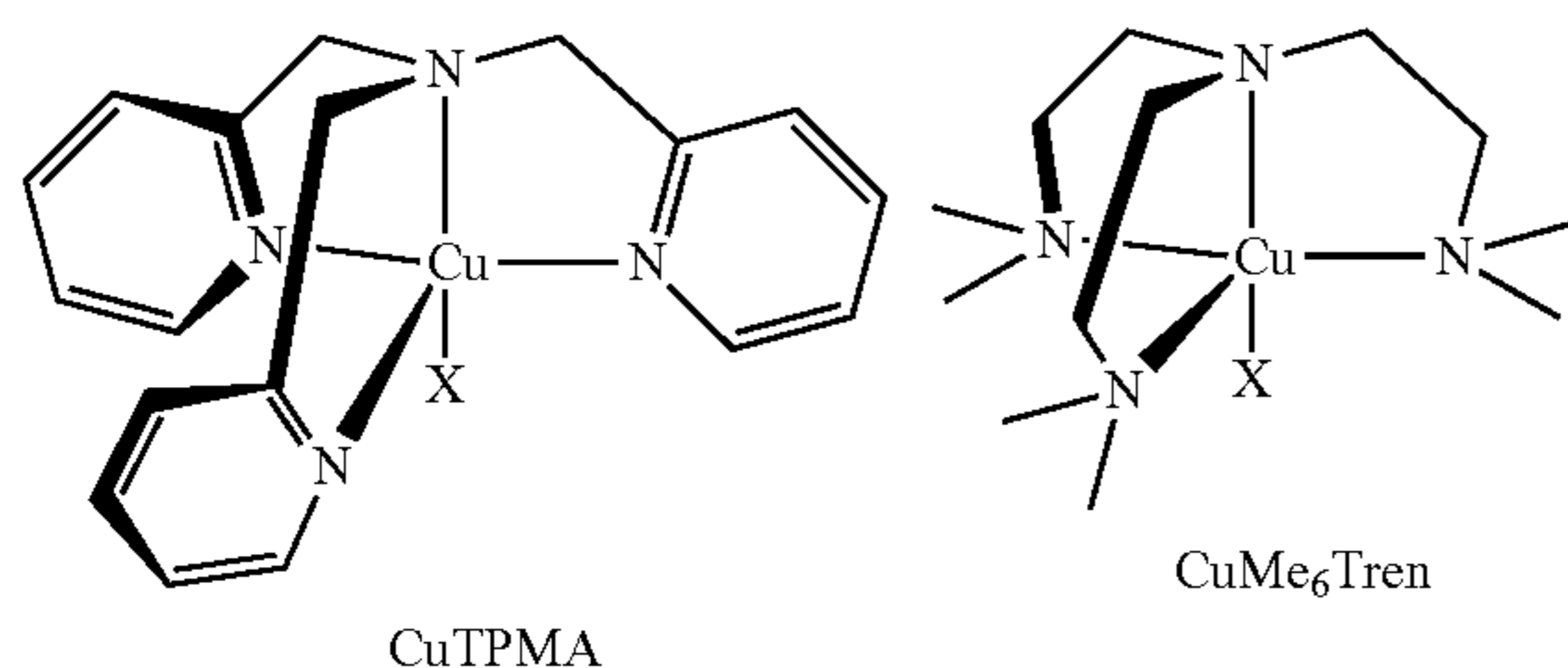
In an example, the source of nitrite ions in the medium **30** may be a water soluble, inorganic nitrite salt in an aqueous solution (e.g., water) or a hydrogel (e.g., hydroxymethylcellulose, poly(vinyl alcohol) (PVA), gelatin, etc.). Some examples of water soluble, inorganic nitrite salts include alkali metal nitrite salts and alkaline earth metal nitrite salts. Specific examples include nitrite salts of Li, Na, K, Rb, Ca, and Mg. Most other metal salts are also soluble in water, for example, Al salts and Fe salts. One specific example of the source of nitrite is sodium nitrite ( $\text{NaNO}_2$ ). It is to be understood that ammonium nitrite or organic ammonium nitrite salts (e.g.,  $\text{R}_4\text{N}^+\text{NO}_2^-$  or  $\text{RNH}_3^+\text{NO}_2^-$ ) could also be used, provided they are soluble in the aqueous phase. Tetramethylammonium nitrite and tetraethylammonium nitrite are specific examples of suitable water soluble, organic ammonium nitrite salts.



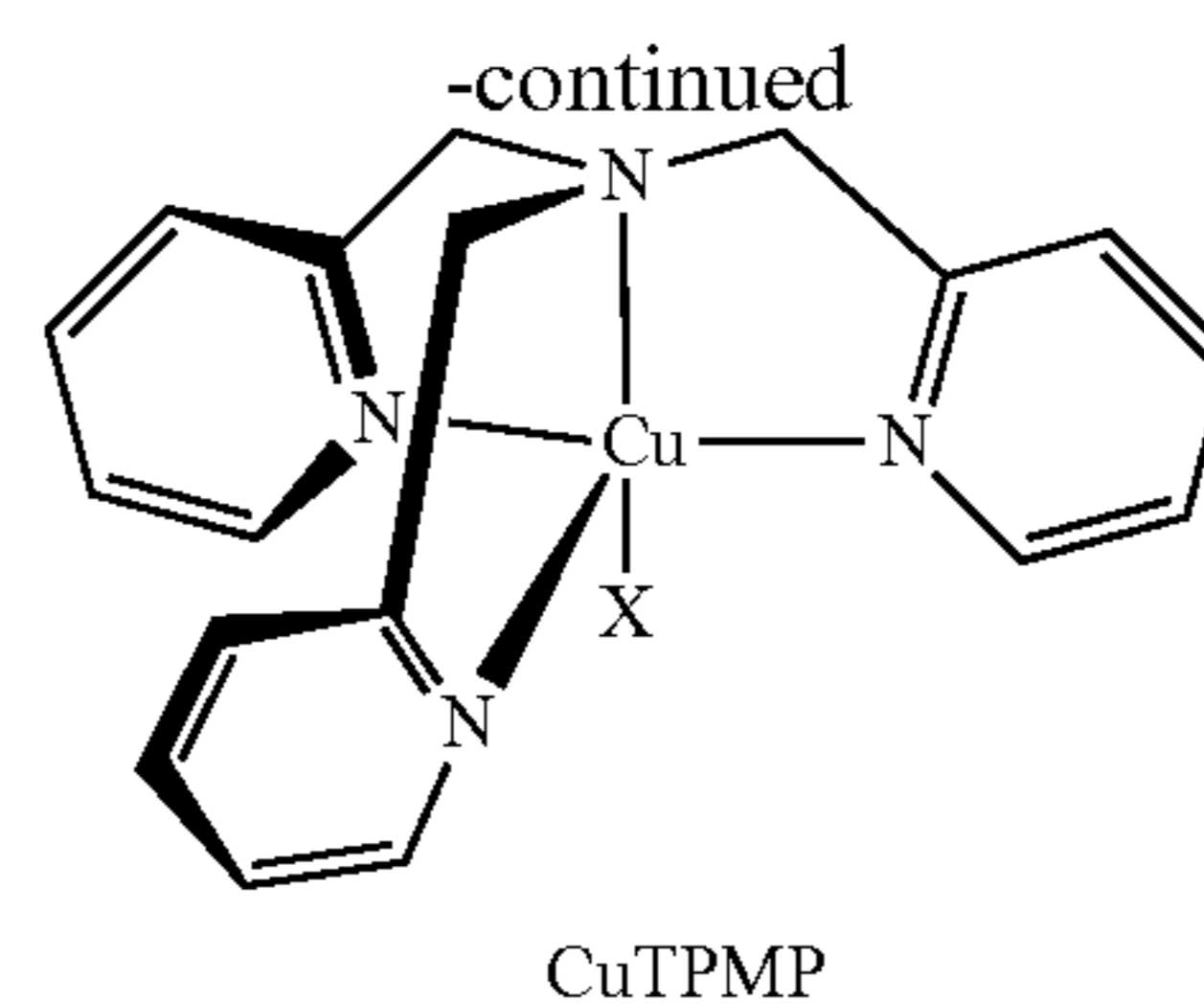
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Using a high concentration of the nitrite salts in the medium **30** may significantly reduce the amount of  $N_2O$  that may be generated during the electrochemical methods disclosed herein. In the examples disclosed herein, at least 100 mM nitrite is used as the medium **30**, and amounts lower than 100 mM are generally not used, in part because higher levels of nitrite result in lower levels of  $N_2O$ . These levels of nitrite suppress the formation of  $N_2O$  to negligible levels. As an example, a medium **30** including 400 mM nitrite may result in less than 5%  $N_2O$  in the total gas species that is generated using the methods disclosed herein. It is believed that the excess nitrite competitively binds to the Cu center of the ligand complex (after the mediated reduction of nitrite to NO by the complex) so that the electrogenerated NO leaves the copper-ligand complex, rather than such a complex being reduced electrochemically again in the presence of another nitrite ion to form  $N_2O$ . This prevents the formation of significant levels of  $N_2O$ .

In addition, in some examples, the medium **30** includes the Cu(II)-ligand complex, which may also be water soluble. Examples of the Cu(II)-ligand complex are selected from the group consisting of Cu(II)-tri(2-pyridylmethyl)amine (CuTPMA), Cu(II)-tri(2-dimethylamino)ethyl]amine (CuMe<sub>6</sub>Tren), Cu(II)-tri(2-pyridylmethyl)phosphine (CuTPMP), Cu(II)-1,4,7-trimethyl-1,4,7-triazacyclononane (Cu(Me<sub>3</sub>TACN)), Cu(II)-1,4,7-triethyl-1,4,7-triazacyclononane (Cu(Et<sub>3</sub>TACN)), Cu(II)-1,4,7-tripropyl-1,4,7-triazacyclononane (Cu(Pr<sub>3</sub>TACN)), Cu(II)-1,4,7-triisopropyl-1,4,7-triazacyclononane (Cu(iPr<sub>3</sub>TACN)), Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-ethylate) (Cu(BMPA-Et)), Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-propanoate) (Cu(BMPA-Pr)), Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-butylate) (Cu(BMPA-Bu)), Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-ethylate) (Cu(BEPA-Et)), Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-propanoate) (Cu(BEPA-Pr)), Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-butylate) (Cu(BEPA-Bu)), Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-methyl-phenolate) (Cu(BMPA-MePhO)), Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-ethyl-phenolate) (Cu(BMPA-EtPhO)), Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-propyl-phenolate) (Cu(BMPA-PrPhO)), Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-methyl-phenolate) (Cu(BEPA-MePhO)), Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-ethyl-phenolate) (Cu(BEPA-EtPhO)), Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-propyl-phenolate) (Cu(BEPA-PrPhO)), Cu(II)-3-((2-(pyridin-2-yl)ethyl)(pyridin-2-ylmethyl)amino)ethylate (Cu(PEMA-Et)), Cu(II)-3-((2-(pyridin-2-yl)ethyl)(pyridin-2-ylmethyl)amino)propanoate (Cu(PEMA-Pr)), Cu(II)-3-((2-(pyridin-2-yl)ethyl)(pyridin-2-ylmethyl)amino)butylate (Cu(PEMA-Bu)), Cu(II)-2-(pyridin-2-yl)-N,N-bis(pyridin-2-ylmethyl)ethan-1-amine (Cu(PMEA)), Cu(II)-2,2'-(2-(2-(pyridin-2-yl)ethyl)butane-1,4-diyl)dipyridine (Cu(PMAP)), and combinations thereof. In a specific example, the Cu(II)-ligand complex may be selected from Cu(II)-tri(2-pyridylmethyl)amine (CuTPMA), Cu(II)-tri(2-dimethylamino)ethyl]amine (CuMe<sub>6</sub>Tren), Cu(II)-tri(2-pyridylmethyl)phosphine (CuTPMP), and combinations thereof. These structures are shown below:

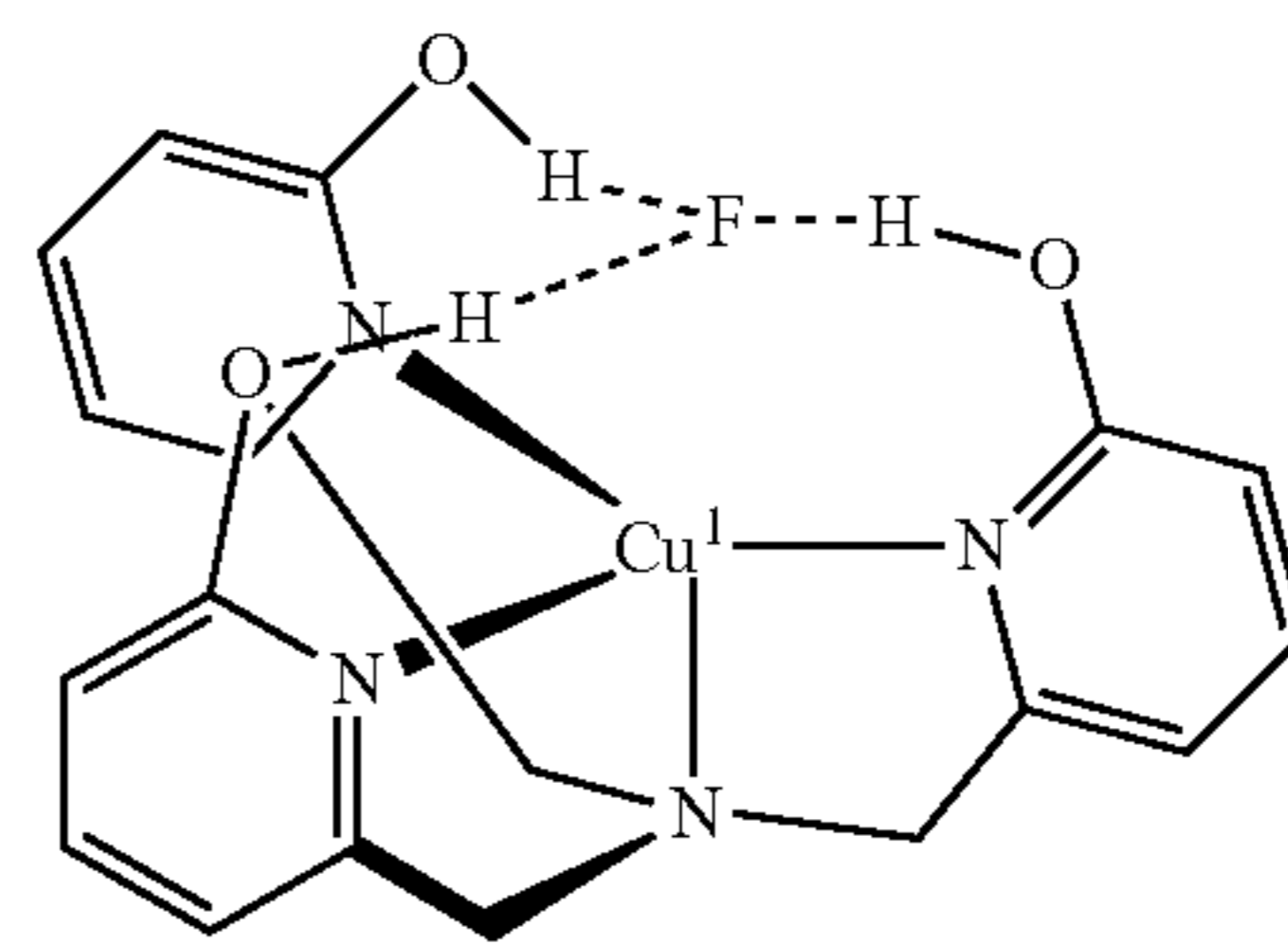


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X = NO<sub>2</sub><sup>-</sup> or H<sub>2</sub>O

While several examples of the Cu(II)-ligand complex are provided herein, it is to be understood that other water soluble Cu(II)-complexes may be used. For example, Cu(II)-complexes that are not water soluble or have poor water solubility (i.e., <1 mM) may be used. An example of a Cu(II)-complex having poor water solubility is CuH<sub>3</sub>thpa:



Any of the Cu(II)-complexes disclosed herein may be immobilized on the surface of the working electrode **14**, rather than being dissolved or dispersed in the medium **30** from the outset of the method. As previously mentioned, the Cu(II)-complexes may be covalently attached to the working electrode **14**, physically adsorbed to the working electrode **14**, or doped in or covalently attached to a polymer, thin film, or hydrogel that is deposited on the working electrode **14**.

Examples of polymers that may be deposited on the working electrode **14** and that may have the Cu(II)-complex doped therein or covalently attached thereto include polyethylenimine, polyvinylimidazole, polypyrrole, polyurethane, or ion exchange membranes (e.g., NAFION<sup>®</sup>, from Dupont). The thin film that may be deposited on the working electrode **14** and that may have the Cu(II)-complex doped therein or covalently attached thereto may be any of those previously described (e.g., gold, platinum, etc.), or a self-assembled monolayer (SAM). Examples of suitable hydrogels that may be deposited on the working electrode **14** and that may have the Cu(II)-complex doped therein or covalently attached thereto may be any of those previously described (e.g., hydroxymethylcellulose, poly(vinyl alcohol) (PVA), gelatin, etc.).

In an example of the medium **30**, the source of nitrite ions is any water soluble, inorganic or organic nitrite salt, and the Cu(II)-ligand complex is any of the examples set forth herein.

The medium **30** may also include a buffer and/or another additive that aids in driving the reduction reaction of Cu(I) with nitrite. Examples of suitable buffers are phosphate buffered saline (PBS), or 3-(N-morpholino)propanesulfonic acid (MOPS), or 4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid (i.e., N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES)). An example of another suitable additive is ethylenediaminetetraacetic acid (EDTA). EDTA



helps drive the reduction reaction of Cu(I) with nitrite ( $\text{Cu(I)} + \text{NO}_2^- + 2\text{H}^+ \rightarrow \text{Cu(II)} + \text{NO} + \text{H}_2\text{O}$ ) to the product side by chelating with Cu(II) stronger than with Cu(I).

Moreover, when a Ag/AgCl reference electrode **16**, **20** is utilized, a fixed level of chloride ions is provided (e.g., as NaCl) in the medium **30** so that the reference electrode **16**, **20** can maintain a constant potential (EMF).

When included in the medium **30**, the Cu(II)-ligand complex may be present in a concentration ranging from about 0.1 mM to about 1 M, and the nitrite may be present in a concentration ranging from about 1 mM to the solubility limit of the nitrite (e.g., about 12 M for  $\text{NaNO}_2$  at room temperature). In an example, a 1 M  $\text{NaNO}_2$  solution may include from about 7 mM of the Cu(II)-ligand complex to about 14 mM of the Cu(II)-ligand complex. When immobilized on the surface of the working electrode **14**, the Cu(II)-ligand complex may be a single monolayer or several layers that extend across the surface of the working electrode **14**.

Each example NO generating system **12**, **12'** may include a reservoir or housing **31**, that contains the medium **30** and the various electrodes **14**, **16** or **14**, **20**, **22**. The housing **31** may be made of any suitable material that can contain the medium **30** and the various electrodes **14**, **16** or **14**, **20**, **22**, and that is not permeable to nitrogen gas  $\text{N}_2$  or to nitric oxide NO. Examples of suitable housing **31** materials include NO impermeable polymers (e.g., polytetrafluoroethylene (PTFE)), glass, etc. The housing **31** may be sealed around an inlet conduit **32** (used to introduce the nitrogen gas  $\text{N}_2$ ) and an outlet conduit **38** (used to transport a stream of nitrogen gas and nitric oxide  $\text{N}_2/\text{NO}$ ). The housing **31** may also be disposable so that the entire gas delivery device **10**, **10'** can be discarded at the end of its useful life, or it can include an opening through which the medium **30** and/or any of the electrodes **14**, **16** or **14**, **20**, **22** can be replaced.

Examples of the method disclosed involve the electrochemical generation of nitric oxide using the nitric oxide generating system **12**, **12'**, and the delivery of the nitric oxide using the gas delivery device **10**, **10'**. Some examples of the method involve applying a cathodic voltage or a cathodic current to the working electrode **14** positioned in contact with the medium **30** including the source of nitrite ions and the Cu(II)-ligand complex, thereby reducing the Cu(II)-ligand complex to a Cu(I)-ligand complex which reacts with nitrite from the source of nitrite ions to generate nitric oxide (NO); sweeping the nitric oxide using nitrogen gas to form a stream of nitrogen gas and nitric oxide; and introducing an oxygen-containing gas to mix with the stream of nitrogen gas and nitric oxide to form an output gas stream. Each of these steps is schematically shown in FIGS. **1A** and **1B**.

Electrochemical generation of nitric oxide using the two-electrode system of FIG. **1A** or the three-electrode system of FIG. **1B** involves immersing the electrodes **14**, **16** or **14**, **20**, **22** in the medium **30**, and applying the cathodic voltage to the working electrode **14** (e.g., using the previously described potentiostatic mode), or applying the cathodic current to the working electrode **14** (e.g., using the previously described galvanostatic mode). The cathodic voltage or current may be applied continuously, in pulses (e.g., more negative voltage followed by less negative voltage), or using a desirable on/off sequence. When applied, the cathodic voltage or cathodic current causes the Cu(II)-ligand complex  $\text{Cu}^{II}\text{L}$  (in the medium **30** and/or on the working electrode **14**) to electrochemically reduce on or near the working electrode **14** surface, which produces a high concentration of the Cu(I)-ligand complex  $\text{Cu}^I\text{L}$  at or near the working electrode **14** surface (as shown in FIG. **1A**,  $\text{Cu}^{II}\text{L} \rightarrow \text{Cu}^I\text{L}$ ). In turn, the

Cu(I)-ligand complex  $\text{Cu}^I\text{L}$  reacts directly with the nitrite ( $\text{NO}_2^-$ ) in the medium **30** to generate nitric oxide gas (NO). In other words, the NO gas is generated by a one electron electrochemical reduction of  $\text{NO}_2^-$  at the working electrode **14** using the Cu(II)-ligand complex  $\text{Cu}^{II}\text{L}$  as an electron transfer mediator. The NO gas levels are produced at a rate dependent upon the applied cathodic voltage or the applied current (as will be described further hereinbelow).

The NO generated in the medium **30** is swept or purged from the medium **30** via a nitrogen gas  $\text{N}_2$  that is introduced into the medium **30** via an inlet conduit **32** of the device **10**, **10'**. The nitrogen gas  $\text{N}_2$  (also referred to herein as the nitrogen purge gas) may be supplied to the inlet conduit **32** from a gas source, such as a compressed gas tank **34** or an oxygen scrubber **36** (both of which are shown and further described in reference to FIG. **2**). As such, it is to be understood that the nitrogen gas  $\text{N}_2$  used to purge the NO from the medium **30** may be at least substantially pure nitrogen gas  $\text{N}_2$  (e.g., delivered from the tank **34**) or may be a mixed gas, which may be derived from ambient air that contains nitrogen gas, argon gas, carbon dioxide, and potentially small amounts of other non-oxygen gases, or may be a mixture of nitrogen gas and other inert gas(es). The nitrogen purge gas  $\text{N}_2$  does not passivate the working electrode **14**, and thus a cleaning process does not need to be performed throughout the electrochemical generation of NO. Moreover, unlike oxygen purge gas, the nitrogen purge gas  $\text{N}_2$  does not react with the Cu(I)-ligand complex  $\text{Cu}^I\text{L}$ , and thus does not reduce the amount of Cu(I)-ligand complex  $\text{Cu}^I\text{L}$  that is generated, and thus, in turn, also does not reduce the amount of NO that is generated. Additionally, the nitrogen purge gas  $\text{N}_2$  does not react with the NO generated on the surface of the working electrode **14**, which can lead to high NO generating efficiency. As such, the use of the nitrogen purge gas  $\text{N}_2$  improves the stability (in terms of NO generation) and the performance of the devices **10**, **10'**, when compared to similar devices that utilize an oxygen purge gas to remove the generated NO from solution.

In the example gas delivery devices **10**, **10'**, the inlet conduit **32** delivers the nitrogen gas  $\text{N}_2$  to the medium **30** in contact with the electrodes **14**, **16** or **14**, **20**, **22**. The inlet conduit **32** may be any suitable polymeric or other tubing attached to the gas source (not shown). The inlet conduit **32** is configured so that the nitrogen gas  $\text{N}_2$  is introduced directly into the medium **30**, and not into any headspace that may be present above the medium **30**. The introduction of the nitrogen gas  $\text{N}_2$  directly into the medium **30** causes bubbles to form in the medium **30** (as shown in FIGS. **1A** and **1B**). The bubbles help mix the medium **30**, and also help purge the NO (that is formed in the medium **30**) out into the exit gas stream of the nitric oxide generating system **12**, **12'**. This exit gas stream is shown as  $\text{N}_2/\text{NO}$ , and is a stream of nitrogen gas and nitric oxide gas.

The stream of nitrogen gas and nitric oxide gas  $\text{N}_2/\text{NO}$  exits the nitric oxide generating system **12**, **12'** through an outlet conduit **38**. In other words, the outlet conduit **38** transports the stream of nitrogen gas and nitric oxide  $\text{N}_2/\text{NO}$  from the medium **30**. The outlet conduit **38** may be a tube that has low or no permeability to at least the nitrogen gas and the nitric oxide. The length of the outlet conduit **38** may also be relatively short in order to avoid loss of gas before the stream is delivered to a desirable destination, such as a separator **42** (FIG. **2**), a nitric oxide extraction device **44** (FIG. **4**), or an oxygenator **46** (FIG. **5**).

In some examples, the stream of nitrogen gas and nitric oxide gas  $\text{N}_2/\text{NO}$  stream may be transported as a result of pressure from the gas source, which may include a regulator



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to control the flow rate. In other examples, the stream of nitrogen gas and nitric oxide gas  $N_2/NO$  stream may be transported as a result of pressure from a vacuum positioned downstream.

As shown in FIGS. 1A and 1B, the gas delivery devices **10**, **10'** include an inspiratory gas conduit **40** operatively connected to the outlet conduit **38** to introduce an oxygen-containing gas OC and form an output gas stream OG of the gas delivery device **10**, **10'**. The oxygen-containing gas OC may be at least substantially pure oxygen gas  $O_2$  or air. The oxygen-containing gas OC mixes with the stream of nitrogen gas and nitric oxide gas  $N_2/NO$  to form an output gas stream OG. In an example, the source (not shown) of the oxygen-containing gas OC may include a regulator to control the flow rate, so that the output gas stream OG contains from about 20% oxygen to about 99.99% oxygen. Since the oxygen-containing gas OC is introduced just prior to delivery to the recipient **48**, the impact on the NO concentration is minimal or nil due to the short contact time between the NO and the oxygen-containing gas OC.

The inspiratory gas conduit **40** may be a tube that has low or no permeability to at least the oxygen-containing gas, the nitrogen gas, and the nitric oxide. Examples of suitable tubing material include poly(vinyl chloride) (PVC), polyurethane (PU), polyethylene (PE), fluorinated polymers, etc.

As will be discussed further in reference to FIGS. 2, 4A, 4B, and 5, examples of the method may also involve transporting the output gas stream OG to a desired destination. While not shown in FIGS. 1A and 1B, it is to be understood that the gas delivery devices **10**, **10'** may further include a delivery conduit **72** that is operatively connected to the outlet conduit **38** and the inspiratory gas conduit **40**. As one example, the delivery conduit **72** may be connected to an exit of the outlet conduit **38** that is downstream of the inspiratory gas conduit **40** so that the gases have time to mix within the outlet conduit **38** before being delivered to the desired destination. Examples of other suitable connections for the delivery conduit **72** are described in reference to FIGS. 2, 4A, and 4B. The delivery conduit **72** may be a hose, tube, or other like conduit that can transport the output gas stream OG to the desired destination (e.g., to a patient through an inhalation unit that is operatively connected to the deliver conduit). The desired destination may be a patient **48** (FIGS. 2, 4A, and 4B) or a blood oxygenator **46** (FIG. 5).

Different examples of the gas delivery device **10'A** and **10'B** (including the three-electrode nitric oxide generating system **12'**) for inhalation therapy are shown, respectively, in FIGS. 2, 4A, and 4B. It is to be understood that these devices could also be made with the two-electrode nitric oxide generating system **12**. As shown in FIG. 5, any of the examples of the gas delivery device **10**, **10'**, **10'A**, **10'B**, **10'C** may be used to add nitric oxide to the sweep gas of a blood oxygenator **46**, thereby helping to prevent platelet and other cell activation in the blood flowing through the oxygenator **46**.

The potentiostat/galvanostat **18** and its associated electronics that are used in the examples shown in FIGS. 2, 4A, 4B, and 5 may be minimized to be secured to one or more components of the nitric oxide generating system **12'** or another component of the gas delivery device **10**, **10'**, **10'A**, **10'B**, and may be operated via a battery or another source of energy (e.g., solar generator, an energy harvesting device, etc.).

Referring now to FIG. 2, one example of the gas delivery device **10'A** is shown for inhalation therapy. This example

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device **10'A** includes the nitric oxide generating system **12'**, and each of its previously described components.

In this example device **10'A**, the nitrogen gas  $N_2$  may be supplied to the inlet conduit **32** from a gas source, such as the compressed gas tank **34** or the oxygen scrubber **36**. Either the compressed gas tank **34** or the oxygen scrubber **36** may be used, and is operatively connected to the inlet conduit **32**. The compressed gas tank **34** may include compressed nitrogen gas  $N_2$ , with a regulator to control the flow rate of the nitrogen gas  $N_2$  to the inlet conduit **32**. The oxygen scrubber **36** may be operatively connected to a pump **52** that introduces ambient air into the oxygen scrubber **36**. The ambient air is directed to a solution or particle bed **50** of the oxygen scrubber **36**, which is capable of removing the oxygen from the ambient air to generate the nitrogen gas  $N_2$  that is delivered to the inlet conduit **32**. As previously noted, the nitrogen gas  $N_2$  may be a mixed gas derived from ambient air, where the mixed gas contains nitrogen gas, argon gas, carbon dioxide, and potentially small amounts of other non-oxygen gases. In an example, the oxygen scrubber removes at least 50% of the oxygen from the air, and thus the mixed gas may include less than 10% of oxygen gas. In another example, the oxygen scrubber removes enough oxygen from the air so that the mixed gas includes 5% or less of oxygen gas.

In this example of the device **10'A**, the inlet conduit **32** delivers the nitrogen gas  $N_2$  to the nitric oxide generating system **12'**, where NO has been electrochemically generated or will electrochemically generated in the manner previously described. The nitrogen purge gas  $N_2$  may be introduced directly into the medium **30**, or it may first pass through a flowmeter **54**, which measures and controls the linear, nonlinear, mass or volumetric flow rate of the nitrogen purge gas  $N_2$ .

The nitrogen purge gas  $N_2$  that is introduced into the system **12'** picks up the nitric oxide that is generated in the medium **30**. The resulting stream of nitrogen gas  $N_2$  and nitric oxide  $N_2/NO$  is then transported out of the system **12'** through the outlet conduit **38** as previously described.

It is to be understood that this gas stream  $N_2/NO$  may include some aerosol droplets, which contain the nitrite salt and, in some instances, the Cu(II)-ligand complex  $Cu^{II}L$ . In some instances, significant levels of aerosol droplets may be present, which is undesirable for various medical applications. The gas stream  $N_2/NO$  may be sent to a separator **42** that at least substantially removes the aerosol droplets.

The separator **42** may be operatively positioned between the outlet conduit **38** and the inspiratory gas conduit **40**. This positioning of the separator **42** enables the aerosol droplets to be removed from gas stream  $N_2/NO$  before it is mixed with the oxygen-containing gas stream OC.

As shown in FIG. 2, the separator **42** includes a housing **56**, which contains a nitric oxide permeable material **58** separating two spaces **60**, **62**. The housing **56** may be made of any material that is not permeable to the gases that are introduced thereto (e.g., nitrogen gas, nitric oxide, oxygen-containing gas).

The separator housing **56** includes two inlets **64**, **64'** and two outlets **66**, **66'**. The first housing inlet **64** operatively connects the outlet conduit **38** to the first space **60**. As such, the gas stream  $N_2/NO$  is directed from the outlet conduit **38** into the first space **60**. Once in the first space **60**, the gas stream  $N_2/NO$  has two paths. Along the first path, some of the gas stream  $N_2/NO$  will diffuse across the nitric oxide permeable material **58** (also referred to herein as the nitric oxide permeable medium **58**) into the second space **62**. However, all of the gas stream  $N_2/NO$  cannot be forced



through the nitric oxide permeable material **58**. As such, the remainder of the gas stream  $N_2/NO$  will be transported along the second path, which leads to the first housing outlet **66** into a waste reservoir **68**.

The gas stream  $N_2/NO$  that diffuses through the nitric oxide permeable material **58** has the aerosol droplets removed therefrom. The nitric oxide permeable material **58** may be a membrane (**98** as shown in FIG. 2) or a bunch of hollow fibers (**98'** as shown in FIGS. 4A, 4B, and 5). The membrane **98** may be made up of several NO permeable microporous fibers (e.g., silicone rubber, porous polytetrafluoroethylene (PTFE), polybutadiene, poly(butadiene co-styrene), polycis-isoprene, polypropylene (PP), etc.) or another material that allows some of the nitric oxide and some of the nitrogen gas  $N_2$  to diffuse through to the second space **62** (i.e., performs the desired gas exchange). These fibers also block the aerosol droplets so that they are not transported through the membrane **98**.

As mentioned above, the diffused gas stream  $N_2/NO$  (shown as  $D(N_2/NO)$ ) enters the second space **62** of the separator **42**. The second space **62** is connected to the second housing inlet **64'** and the second housing outlet **66'**. The second housing inlet **64'** is also operatively connected to the inspiratory gas conduit **40** to receive, in the second space **62**, the oxygen-containing gas OC, which mixes with the nitric oxide diffusing through the nitric oxide permeable material **58** to form the output gas stream OG. The oxygen-containing gas OC may be delivered to the second space **62** from any suitable gas source **70**, which can regulate the flow of the oxygen-containing gas OC or can be coupled to a flow controller to regulate the flow of the oxygen-containing gas OC. The flow rate of the oxygen-containing gas OC may be continuous or intermittent, and may also depend upon the composition of the oxygen-containing gas OC and the desired fraction of inspired oxygen (i.e.,  $FiO_2$ ). As example, the gas source **70** may be a compressed gas cylinder, a gas pump that delivers ambient air, or any other suitable gas source.

In the second space, diffused gas stream  $D(N_2/NO)$  mixes with the oxygen-containing gas OC to form the output gas stream OG.

A housing output conduit **72'**, which is an example of the previously mentioned delivery conduit **72**, is operatively connected to the second housing outlet **66'** to transport the output gas stream OG to a recipient/patient **48**. The housing output conduit **72'** may be any suitable polymeric or other tubing that is impermeable to the output gas stream OG. In an example, the housing output conduit **72'** has a one-way valve so that the output gas stream OG does not flow back into the separator **42**.

In the example shown in FIG. 2, an inhalation unit **74** may be connected to the housing output conduit **72'** to deliver at least some of the output gas stream OG to the recipient/patient **48**. The inhalation unit **74** may be a ventilator, a face mask, a nasal cannula, or some other suitable apparatus for delivering the output gas stream OG to the airways of the patient.

A sensor **76** may be positioned in contact with the output gas stream OG. The sensor **76** may be positioned in the housing output conduit **72'**, or in another conduit **78** that is split or branched off of the housing output conduit **72'**. When the other conduit **78** is used, it receives at some of the output gas stream OG and transports it to the sensor **76**. In some instances, it may be desirable to position the sensor **76** close to the gas source **70**, where the oxygen-containing gas OC is introduced. In some other instances, it may be desirable to position the sensor **76** close to the inhalation unit **74** (e.g.,

within about 3 feet of the inhalation unit). While not shown, it is to be understood that in still other instances, the device **10'B** may have two sensors **76**, one close to the gas source **70** where the oxygen-containing gas OC is introduced, and another one close to the inhalation unit **74** (e.g., to ensure the stream entering the patient **48** has higher levels of NO and lower levels of  $NO_2$ ).

The sensor **76** may be used to monitor the NO levels in the output gas stream OG. It may be desirable to monitor the NO level in order to avoid forming  $NO_2$  (nitrogen dioxide, which can be generating from  $O_2$  reacting with NO and can be toxic to the recipient/patient **48**). Any suitable NO sensor **76** may be used.

In an example, the sensor **76** is a Shibuki-style sensor (not shown), which is based on the oxidation of NO to nitrate ( $NO_3^-$ ) at an inner platinum (Pt) electrode position behind a gas permeable membrane.

Another example of the sensor **76** is shown in FIG. 3. This sensor **76** is an amperometric NO sensor. The sensor **76** shown in FIG. 3 exhibits relatively rapid response times, and the high surface area of the working electrode(s) **80** yields larger currents than the Shibuki configuration.

As shown in FIG. 3, this example of the sensor **76** includes working electrode(s) **80** (e.g., platinum, gold, etc.) directly deposited (e.g., by chemical reduction) on the surface of a polymer electrolyte (i.e., ionomer film **82**). Examples of the ionomer film **82** are a sulfonated tetrafluoroethylene based fluoropolymer-copolymer, such as NAFION® (from DuPont). This example of the sensor **76** also includes a reference electrode **86** and a counter electrode **88**, which are immersed in an inner electrolyte solution **84** that also wets the ionomer phase **82**.

The portion of the output gas stream OG transported through the conduit **78** flows over the surface of the working electrode(s) **80**. A positive potential is applied (e.g., about 1V versus Ag/AgCl), and electrochemical reactions occur at the interface of the working electrode(s) **80** and the ionomer film **82**. In an example, the positive potential applied to the working electrode(s) **80** ranges from about 0.7 V to about 1.1 V. A higher voltage may undesirably cause water oxidation. More specifically, the NO in the output gas stream OG electrochemically oxidizes to nitrite/nitrate to output current signals proportional to  $NO_{(g)}$  levels.

In other examples, the sensor **76** can include another working electrode (not shown) on the same surface of the ionomer film **82** as the working electrode(s) **80**, and a less positive potential may be applied to that other working electrode so that only  $NO_2$  is oxidized (not NO) and sensed (via current measured). The NO sensor signal can be corrected for any  $NO_2$  present using a bipotentiostat.

The sensor **76** data (i.e., the concentration of NO in the output gas stream OG and/or the concentration of  $NO_2$  in the output gas stream OG) may be used to servo-regulate the potential or current applied to the NO generating system **12**, **12'** to achieve an at least substantially constant concentration of NO at the delivery end. The data may also be used to regulate the flow of the output gas stream OG.

When the sensor **76** data indicates that the NO level is too high or too low, the applied potential or current may be adjusted and/or the flow rate of one or more of the gases may be adjusted. In an example of the method, the sensor **76** monitors a nitric oxide level of the output gas stream OG, and based on the nitric oxide level of the output gas stream OG, the potentiostat/galvanostat **18** one of: maintains the applied cathodic voltage or current (e.g., when the NO is at a desired level); or adjusts the applied cathodic voltage or current to increase NO production (e.g., when the nitric



oxide level of the output gas stream OG is below a target level); or adjusts the applied cathodic voltage or current to decrease NO production (e.g., when the nitric oxide level of the output gas stream OG is above the target level). When the sensed NO level is too low, a more negative potential (that is also more positive than the cathodic potential that causes water reduction) or an increased cathodic current (that is below a limiting current) may be applied. When the sensed NO level is too high, a less negative (i.e., more positive) potential or a decreased cathodic current may be applied. As an example, the voltage may be modulated to be more or less negative in order to increase or decrease, respectively, the rate of NO production, and thus the flux of NO swept from the NO generating device **12**, **12'** and present in the output gas stream OG.

The target level may be based upon the given application in which the NO is being used. The target level may be very low or very high, depending upon the patient and the application. As examples, the target level of NO for a newborn on inhalation therapy may range from about 10 ppm to about 70 ppm, and the target level of NO to be generated in an oxygenator to prevent activation of platelets and other cells during bypass surgery may range from about 190 ppm to about 210 ppm. Further, for antimicrobial applications, such as for lung infections, lower levels of NO may be useful for inhalation therapy, in the range of, for example, from about 500 ppb to about 10 ppm.

The sensor **76** data may be used to determine whether a modulation in the flux of the generated NO is desirable. Several techniques may be used to modulate the flux, including altering an amount of a surface area of the working electrode **14** that is exposed to the medium **30**, and/or altering a concentration of any of the Cu(II)-ligand complex  $\text{Cu}^{\text{II}}\text{L}$  or the source of nitrite ions, and/or altering a magnitude of the cathodic voltage over time (as previously described), and/or altering a magnitude of the cathodic current over time (as previously described). Increasing the surface area of the working electrode **14** will increase the NO production rate, while decreasing the surface area of the working electrode **14** will decrease the NO production rate. In some examples, the concentration of the Cu(II)-ligand complex  $\text{Cu}^{\text{II}}\text{L}$  may be varied from about 1 mM to about 10 mM and/or the concentration of the source of nitrite ions may be varied from about 50 mM to about 1 M. Increasing the concentrations of both the Cu(II)-ligand complex  $\text{Cu}^{\text{II}}\text{L}$  and the source of nitrite ions is expected to increase the NO production rate, while decreasing the concentrations of both the Cu(II)-ligand complex  $\text{Cu}^{\text{II}}\text{L}$  and the source of nitrite ions is expected to decrease the NO production rate. When altering the magnitude of the cathodic voltage, more negative potentials (before reaching limiting current) should increase the NO production rate. When altering the magnitude of the cathodic current, higher current (but below limiting current) should increase the NO production rate.

The sensor **76** data may also be used to determine whether an undesirable amount of  $\text{NO}_2$  is present in the output gas stream OG. If an undesirable amount of  $\text{NO}_2$  is present, an alarm on the device **10'A** may be initiated and/or the applied voltage and/or current may be adjusted to reduce the NO delivery from the system **12'**. Moreover, a soda lime scrubber may be included in the inhalation unit **74**, just before the output gas stream OG is delivered to the patient **48**. If the  $\text{NO}_2$  content is greater than 1 ppm in the final gas phase, the soda lime scrubber can remove the excess  $\text{NO}_2$ .

Referring now to FIGS. **4A** and **4B**, two examples of the gas delivery device **10'B** and **10'C** for inhalation therapy are respectively depicted. Each example device **10'B**, **10'C**

includes the nitric oxide generating system **12'**, and each of its previously described components. Each example device **10'B**, **10'C** also includes a nitric oxide extraction device **44** (the components of which are described below), and a fluid recirculation system **100** connecting the housing **31** of the nitric oxide generating system **12'** to a housing **90** of the nitric oxide extraction device **44**.

In these examples, the nitric oxide is electrochemically generated in the solution **30** as previously described. The solution **30'**, which has dissolved electrochemically generated nitric oxide therein, is then circulated through a fluid recirculation system **100** to a nitric oxide extraction device **44** for extraction of the nitric oxide from the solution **30'**. The fluid recirculation system **100** fluidly connects the nitric oxide generating system **12'** to the nitric oxide extraction device **44**. As used herein, the term "fluidly connect," means that two spatial regions are connected together such that a liquid (and any gas(es) dissolved therein) may flow between the two spatial regions. As an example, a first conduit A of the fluid recirculation system **100** fluidly connects an outlet in the housing **31** of the nitric oxide generating system **12'** to an inlet of a housing **90** of the nitric oxide extraction device **44**.

The nitric oxide extraction device **44** may be operatively positioned along the fluid recirculation system **100**. As shown in FIGS. **4A** and **4B**, the nitric oxide extraction device **44** includes the housing **90**, which contains a nitric oxide permeable material/medium **58** positioned therein. The housing **90** may be made of any material that is not permeable to the gases that are introduced thereto (e.g., nitrogen gas, nitric oxide and/or oxygen-containing gas).

Within the housing **90**, a space at least partially surrounds the nitric oxide permeable material **58**. The space includes an input area **92**. The input area **92** receives the nitric oxide-containing solution **30'** from the nitric oxide generating system **12'** through the first conduit A of the fluid recirculation system **100**. As used herein, the phrase "nitric oxide-containing solution" refers to the medium/solution having the generated nitric oxide dissolved therein. The space also includes an output area **94**. The output area **94** transports an at least substantially reduced nitric oxide solution **30''** out of the nitric oxide extraction device **44** through a second conduit B of the fluid recirculation system **100**. As used herein, the phrase "at least substantially reduced nitric oxide-containing solution" refers to the medium/solution after at least some of the nitric oxide removed therefrom, and thus the concentration of NO in the at least substantially reduced nitric oxide-containing solution **30''** is less than the concentration of NO in the nitric oxide-containing solution **30'**. As such, both solutions **30'**, **30''** include the source of nitrite ions, and in some instances, the Cu(II)-ligand complex  $\text{Cu}^{\text{II}}\text{L}$  (i.e., when it is in the medium **30** and not immobilized on the working electrode **14**), but solution **30''** includes less nitric oxide than the solution **30'**.

The nitric oxide-containing solution **30'** is directed from a conduit A of the fluid recirculation system **100** into the input area **92**. Once in the input area **92**, at least some of the nitric oxide will diffuse out of the solution **30'** and across the nitric oxide permeable material **58**. The remaining solution **30''** (which now has a lower nitric oxide concentration) will be transported/circulated on the outside of the nitric oxide permeable material **58**, which leads to the output area **94** and into the other conduit B of the fluid recirculation system **100**.

The conduit B of the fluid recirculation system **100** connects an outlet of the housing **90** to an inlet of the housing **31** of the nitric oxide generating system **12'**. A pump



53 may be operatively connected along the conduit B. An example of the pump 53 is a centrifugal type pump. The pump 53 enables the solution 30' to transport, in a single direction, through the first conduit A into the nitric oxide extraction device 44 and enables the at least substantially reduced nitric oxide solution 30" to transport, in the single direction, through the second conduit B and into the nitric oxide generating system 12'. The pump 53 may circulate the medium, 30',30" at a liquid flow rate ranging from about 170 mL/min to about 535 mL/min. The nitric oxide solution 30" may be reused in the nitric oxide generating system 12' to generate additional NO and form the solution 30'. The conduits A and B may be any of the gas impermeable materials disclosed herein.

The nitric oxide that diffuses through the nitric oxide permeable material 58 is separated from the remainder of the solution 30". In this example, the nitric oxide permeable material 58 may be a bunch of hollow fibers 98'. Each hollow fiber 98' may be made up of silicone rubber, porous polytetrafluoroethylene (PTFE), polybutadiene, poly(butadiene co-styrene), polycisoprene, polypropylene (PP), or another material that allows some of the nitric oxide to diffuse therethrough.

In these examples, the nitric oxide extraction device 44 includes an inlet conduit 32' that delivers a sweep gas SG to the nitric oxide permeable material 58. The sweep gas SG is selected from the group consisting of nitrogen gas N<sub>2</sub>, an oxygen-containing gas, and combinations thereof. The nitric oxide extraction device 44 also includes an outlet conduit 72' or 72" that transports a mixed gas stream from the nitric oxide permeable medium 58. The mixed gas stream includes nitric oxide and the sweep gas SG. As such, in some examples the mixed gas includes N<sub>2</sub>/NO as shown in FIG. 4A, and in other examples, the mixed gas includes the output gas stream OG as shown in FIG. 4B.

In the example device 10'B shown in FIG. 4A, the nitrogen gas N<sub>2</sub> is the sweep gas SG that is delivered to the nitric oxide permeable material 58. Similar to the device 10'A, the nitrogen gas N<sub>2</sub> in this example device 10'B may be supplied to the inlet conduit 32' from a gas source, such as the compressed gas tank 34 or the oxygen scrubber 36. Either the compressed gas tank 34 or the oxygen scrubber 36 may be used, and is operatively connected to the inlet conduit 32'. The compressed gas tank 34 may include compressed nitrogen gas N<sub>2</sub>, with a regulator to control the flow rate of the nitrogen gas N<sub>2</sub> to the inlet conduit 32. The oxygen scrubber 36 may be operatively connected to a pump 52 that introduces ambient air into the oxygen scrubber 36. The ambient air is directed to a solution or particle bed 50 of the oxygen scrubber 36, which is capable of removing the oxygen from the ambient air to generate the nitrogen gas N<sub>2</sub> that is delivered to the inlet conduit 32'. As previously noted, the nitrogen gas N<sub>2</sub> may be a mixed gas derived from ambient air, where the mixed gas contains nitrogen gas, argon gas, carbon dioxide, and potentially small amounts of other non-oxygen gases, or may be a mixture of nitrogen gas and other inert gas(es).

In this example of the device 10'B shown in FIG. 4A, the inlet conduit 32' delivers the nitrogen gas N<sub>2</sub> to the nitric oxide permeable material 58, where NO (diffused from the solution 30') is crossing the fibers 98'. The nitrogen purge gas N<sub>2</sub> may be introduced directly into the nitric oxide permeable material 58, or it may first pass through a flowmeter 54, which measures and controls the linear, nonlinear, mass or volumetric flow rate of the nitrogen gas N<sub>2</sub>.

The nitrogen gas N<sub>2</sub> that is introduced into the nitric oxide extraction device 44 picks up the nitric oxide that is crossing the nitric oxide permeable material 58. The resulting stream of nitrogen gas N<sub>2</sub> and nitric oxide N<sub>2</sub>/NO is then transported out of the nitric oxide extraction device 44 through the outlet conduit 38'.

It is to be understood that this gas stream N<sub>2</sub>/NO includes no solution 30', as the fibers 98 block the solution 30' so that it is not transported through the material 58.

The outlet conduit 38' is also operatively connected to the inspiratory gas conduit 40 to receive the oxygen-containing gas OC, which mixes with the gas stream N<sub>2</sub>/NO to form the output gas stream OG. The oxygen-containing gas OC may be delivered from any suitable gas source 70 (e.g., compressed gas cylinder, gas pump that delivers ambient air, etc.), which can regulate the flow of the oxygen-containing gas OC or can be coupled to a flow controller to regulate the flow of the oxygen-containing gas OC. The flow rate of the oxygen-containing gas OC may be continuous or intermittent, and may also depend upon the composition of the oxygen-containing gas OC and the desired fraction of inspired oxygen (i.e., FiO<sub>2</sub>).

In the outlet conduit 38', the gas stream N<sub>2</sub>/NO mixes with the oxygen-containing gas OC to form the output gas stream OG.

A delivery conduit 72' is operatively connected to the outlet conduit 38' to transport the output gas stream OG to a recipient/patient 48. The delivery conduit 72' may be any suitable polymeric or other tubing that is impermeable to the output gas stream OG. In an example, the delivery conduit 72' has a one-way valve so that the output gas stream OG does not flow back into the nitric oxide extraction device 44. It is to be understood that the delivery conduit 72' and the outlet conduit 38' of FIG. 4A may be separate tubes that are operatively connected to one another, or may be a single tube.

In the example device 10'C shown in FIG. 4B, the oxygen-containing gas OC (i.e., O<sub>2</sub> or ambient air) is the sweep gas SG that is delivered to the nitric oxide permeable material 58. In this example, the oxygen-containing gas OC may be delivered from any suitable gas source (e.g., compressed gas cylinder 34', gas pump 52 that delivers ambient air, etc.), which can regulate the flow of the oxygen-containing gas OC or can be coupled to a flow controller to regulate the flow of the oxygen-containing gas OC into the inlet conduit 32'. In an example, 100% air saturation may be used, which corresponds to about 10 mg/L (ppm) of O<sub>2</sub> in the output gas stream OG.

In this example, the oxygen-containing gas OC alone may be used, or it may be mixed with the nitrogen gas N<sub>2</sub>. While not shown, it is to be understood that when the nitrogen gas N<sub>2</sub> is introduced with the oxygen-containing gas OC, the gas delivery device 10'C may also include a compressed gas tank 34 introduces the nitrogen gas N<sub>2</sub> into the inlet conduit 32'.

In this example of the device 10'C shown in FIG. 4B, the inlet conduit 32' delivers the oxygen-containing gas OC to the nitric oxide permeable material 58, where NO (diffused from the solution 30') is crossing the fibers 98'. In this example, the oxygen-containing gas OC acts as the purge gas, and may be introduced directly into the nitric oxide permeable material 58, or it may first pass through a flowmeter 54, which measures and controls the linear, nonlinear, mass or volumetric flow rate of the oxygen-containing gas OC.

The oxygen-containing gas OC that is introduced into the nitric oxide extraction device 44 picks up the nitric oxide



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that is crossing the nitric oxide permeable material **58**. In this example, the resulting gas stream is the output gas stream OG because it contains nitric oxide and the oxygen-containing gas OC (with or without the nitrogen gas N<sub>2</sub>). It is to be understood that output gas stream OG includes no solution **30'**, as the fibers **98'** block the solution **30'** so that it is not transported through the material **58**.

The output gas stream OG is then transported out of the nitric oxide extraction device **44** through the delivery conduit **72"** (which in this example is the outlet conduit **38'**).

Since the oxygen-containing gas OC is introduced as the purge gas in this example, the gas delivery device **10'C** does not include the inspiratory gas conduit **40** or the gas source **70** operatively connected to the delivery conduit **72"**.

The delivery conduit **72"** is capable of transporting the output gas stream OG to a recipient/patient **48**. The delivery conduit **72"** may be any suitable polymeric or other tubing that is impermeable to the output gas stream OG. In an example, the delivery conduit **72"** has a one-way valve so that the output gas stream OG does not flow back into the nitric oxide extraction device **44**.

In the example shown in FIGS. **4A** and **4B**, an inhalation unit **74** may be connected to the respective delivery conduit **72',72"** to deliver at least some of the output gas stream OG to the recipient/patient **48**. The inhalation unit **74** may be a ventilator, a face mask, a nasal cannula, or some other suitable apparatus for delivering the output gas stream OG to the airways of the patient.

The sensor **76** may be positioned in contact with the output gas stream OG. The sensor **76** may be positioned in the delivery conduit **72',72"**, or in another conduit **78** that is split or branched off of the delivery conduit **72',72"**. When the other conduit **78** is used, it receives at some of the output gas stream OG and transports it to the sensor **76**. In some instances, it may be desirable to position the sensor **76** close to the inhalation unit **74** (e.g., within about 3 feet of the inhalation unit). The sensor **76** may be used to monitor the NO levels in the output gas stream OG in the same manner as previously described. The data from the sensor **76** may be used to adjust the applied potential or current and/or the flow rate of one or more of the gases.

In the examples shown in FIGS. **2** and **4A**, the gas stream N<sub>2</sub>/NO may have NO ranging from about 100 ppmv to about 400 ppmv. In the examples shown in FIGS. **2**, **4A**, and **4B**, the output gas stream OG (including the oxygen-containing gas OC) may have NO levels ranging from about 0.1 ppmv to about 400 ppmv.

Referring now to FIG. **5**, any example of the gas delivery device **10**, **10',10'A**, **10'B**, **10'C** is shown as part of an oxygenator **46**. The output gas stream OG may be generated as previously described and may be transported to the conduit **72**, **72',72"**. The length of the conduit **72**, **72',72"** may be relatively short in order to avoid loss of gas before the stream is delivered to the oxygenator **46**.

The conduit **72**, **72',72"** is configured to transport the output gas stream OG of oxygen gas, nitrogen gas and nitric oxide or oxygen gas and nitric oxide from the gas delivery device **10**, **10',10'A**, **10'B**, **10'C** to an oxygenator **46**, which includes the hollow fibers **98'**, which are capable of filtering and cleaning the gas stream OG. In this particular example, the oxygenator **46** is a blood oxygenator, which includes a housing **96** with a blood inlet, a blood outlet, a gas inlet, and a gas outlet (leading to waste **68**).

The gas inlet of the housing **96** is operatively connected to the conduit **72**, **72',72"**. More particularly, the gas inlet directs the output gas stream OG from the conduit **72**, **72',72"** into fibers **98'** that are contained within the housing

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**96**. In this example, each fiber **98'** is a hollow polymeric fiber having a first or interior surface I and a second or exterior surface E. A single blood oxygenator housing **96** may include thousands of hollow polymeric fibers. The output gas stream OG is introduced adjacent to the first or interior surface I. The walls of the hollow polymer fibers act as filters, allowing only the oxygen-containing gas, in some instances the nitrogen gas, and the nitric oxide from the output gas stream OG to permeate therethrough (while trapping contaminants therein). As such, the cleaned output gas stream OG exits from the second or exterior surface E into any blood contained within the housing **96** (as shown in the expanded portion of FIG. **5**). Any of the cleaned output gas stream OG that does not exit into the blood will be directed to the waste reservoir **68**.

The NO in this example serves to locally prevent platelet adhesion and activation on the second or exterior surface E of the fibers **98**. NO coming through the fibers **98** of the oxygenator **46** into the blood can also inhibit activation of white blood cells. The effect of the NO is localized since it reacts immediately with oxyhemoglobin to form met-hemoglobin. When the blood exits the oxygenator **46**, NO is no longer present in the cleaned stream. As such, the blood, containing a cleaned stream of oxygen gas and potentially nitrogen gas N<sub>2</sub>, can then exit the housing **46** and be delivered to a patient **48** (not shown in FIG. **5**).

It is to be understood that various other configurations may be utilized, for example, the blood oxygenator **46** may have a different design.

While several examples of the gas delivery device **10**, **10',10'A**, **10'B**, **10'C** are depicted, it is to be understood that various other configurations may be utilized. For example, a single polymer tube may form the inlet conduit **32** and the outlet conduit **38**, and may be positioned within the medium **30** where NO is generated. In this example, the polymer tube would be permeable to the NO, and the stream of nitrogen gas N<sub>2</sub> transported through the tube would pick up the NO through the permeable tube (i.e., NO would diffuse through the polymer tubing and join the gas stream).

In the examples of the method disclosed herein, the cathodic voltage or cathodic current may be applied to the working electrode **14** for any time interval up to, for example, 30 days. In some instances, it is believed that the voltage or current may be applied continuously for even longer than 30 days. When it is desired to stop generating NO, the cathodic voltage or current is no longer applied to the electrode **14**. The NO release lifetime may be longer when larger reservoir volumes of the medium **30** are used, when higher concentrations of the source of nitrite ions are used, and/or when greater NO conversion efficiency is achieved.

Also in the examples of the method disclosed herein, any suitable gas flow rate may be used. As an example, the flow rate of the nitrogen gas N<sub>2</sub> and/or the oxygen-containing gas OC may range from about 50 mL/min to about 5 L/min.

To further illustrate the present disclosure, examples are given herein. It is to be understood that these examples are provided for illustrative purposes and are not to be construed as limiting the scope of the present disclosure.

## EXAMPLES

### Example 1

An aqueous medium was prepared with 2 mM Cu(II) TPMA, 100 mM sodium nitrite and 0.1 M MOPS buffer (the solution was buffered to pH 7.2). The NO was generated by



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applying a particular voltage for a particular time. The working electrode was a 0.071 cm<sup>2</sup> glassy carbon electrode, the counter electrode was a platinum wire, and the reference electrode was Ag/AgCl. The modulation of NO generation was performed by applying -0.2 V, then -0.3 V, then -0.4 V (vs. 3 M Cl<sup>-</sup> Ag/AgCl reference electrode). The solution was bubbled with N<sub>2</sub> to purge the NO produced. The resulting gas phase was analyzed for NO content using chemiluminescence. The results are shown in FIG. 6. These results illustrate that by applying different cathodic potentials to the working electrode, different levels of NO in the gas phase can be produced even with a small area working electrode. The higher cathodic voltage yielded higher gas phase NO levels.

## Example 2

An aqueous medium was prepared with 2 mM Cu(II) TPMA, 0.4 M sodium nitrite and 0.2 M HEPES buffer (the solution was buffered to pH 7.2). The NO was generated by applying a particular voltage for a particular time. The working electrode had a larger area than the working electrode used in Example 1. In particular, the working electrode was a 2.5×3.5 cm gold mesh electrode (i.e., active surface of about 15 cm<sup>2</sup>), the counter electrode was a large (~25 cm<sup>2</sup>) platinum mesh electrode, and the reference electrode was Ag/AgCl. The modulation of NO generation was performed by applying -0.4 V, then -0.26 V, then -0.24 V, then -0.22 V, then -0.20 V, then -0.17 V (all vs. 3 M Cl<sup>-</sup> Ag/AgCl reference electrode), and then the potential was turned off. The solution was bubbled with N<sub>2</sub> (at a rate of 0.2 L/min) to purge the NO produced. The resulting gas phase was analyzed for NO content using chemiluminescence. The results are shown in FIG. 7. When comparing FIGS. 6 and 7, much higher levels of NO were generated when using the larger area working electrode. The results with the larger area working electrode also illustrate that by applying different cathodic potentials to the working electrode, different levels of NO in the gas phase can be produced, and that higher cathodic voltages yield higher gas phase NO levels.

## Example 3

The NO levels were detected using an amperometric sensor similar to the one shown in FIG. 3. The sensor included a gold working electrode deposited on a NAFION® membrane (i.e., the ionomer phase). The generated gas stream (including NO) was directed over the surface of the working electrode, and the electrochemical oxidation of NO occurred at the interface of the metal working electrode and the ionomer phase which was wetted from an inner electrolyte solution (0.5 M H<sub>2</sub>SO<sub>4</sub>). This sensor exhibited rapid response to the gas phase NO, as shown in FIG. 8), with a linear response from 5 ppbv-600 ppmv NO.

## Example 4

An aqueous medium was prepared with 7 mM Cu(II) Me<sub>3</sub>TACN, 1 M sodium nitrite and 0.5 M HEPES buffer (the solution was buffered to pH 7.3). The NO was generated by applying constant voltages at different times. The working electrode was a 25 cm<sup>2</sup> gold mesh electrode, the counter

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electrode was platinum, and the reference electrode was Ag/AgCl. The modulation of NO generation was performed by continuously adjusting the voltage to apply constant currents of 1 mA, 6 mA, 1.2 mA, 12 mA, and 18 mA for different time periods. The solution was bubbled with N<sub>2</sub> (at a rate of 1 L/min) to purge the NO produced. The resulting gas phase was analyzed for NO content using chemiluminescence. The results are shown in FIG. 9. As illustrated, higher levels of NO were generated when the current was increased. The results also indicate that a substantially constant level of NO can be generated with the constant current method.

## Example 5

An aqueous medium was prepared with 7 mM Cu(II) Me<sub>3</sub>TACN, 1 M sodium nitrite and 0.5 M HEPES buffer (the solution was buffered to pH 7.3). The NO was generated by applying constant currents at different times. The working electrode was a 25 cm<sup>2</sup> gold mesh electrode, the counter electrode was platinum, and the reference electrode was Ag/AgCl. The modulation of NO generation was performed by continuously adjusting the voltage to apply constant currents of 0.5 mA, 1 mA, 2 mA, 3.5 mA, and 5 mA for different time periods. The solution was bubbled with N<sub>2</sub> (at a rate of 1 L/min) to purge the NO produced. A constant stream of 20% oxygen was added to the N<sub>2</sub>/NO gas stream. The resulting gas phase was analyzed for NO content using chemiluminescence. The results are shown in FIG. 10A. As illustrated, higher levels of NO were generated when the current was increased. The results also indicate that a substantially constant level of NO can be generated with the constant current method. In FIG. 10B, the NO measurements are plotted versus the current that was applied. As illustrated, about 9.6 ppm of NO was released for every 1 mA of applied current.

## Example 6

Aqueous solutions were prepared with 7 mM Cu(II) Me<sub>3</sub>TACN, 1 M sodium nitrite and 0.5 M HEPES buffer (the solution was buffered to pH 7.3). The working electrode was a 4.5×8.5 cm<sup>2</sup> gold mesh electrode, and the reference/counter electrode was a 4×4 cm<sup>2</sup> gold electrode. The generation of NO and the modulation of NO generation were performed by continuously adjusting the voltage to apply constant currents of 5 mA, 10 mA, 20 mA, and/or 30 mA for different time periods.

The solution containing the generated NO was pumped into a fiber bundle, where NO diffused through the fibers and excess solution was recirculated back into the container used for NO generation. Air was introduced into the fiber bundle as the sweep gas. In Example A, the sweep gas was introduced at a rate of 0.05 L/min. In Example B, the sweep gas was introduced at a rate of 0.1 L/min. In Example C, the sweep gas was introduced at a rate of 0.2 L/min. The resulting gas phase (containing air and NO) for each example at various currents was analyzed for NO content using chemiluminescence. The results are shown in Table 1.



TABLE 1

	EXAMPLE A			EXAMPLE B			EXAMPLE C	
Air Sweep Gas Rate (L/min)	0.05	0.05	0.05	0.1	0.1	0.1	0.2	0.2
Current (mA)	5	10	20	5	10	30	5	10
NO (ppm)	317	430	>500	196	262	406	103	168

For each of Examples A, B, and C, higher levels of NO were generated when the current was increased. The results also indicate that the resulting gas phase has a higher concentration of NO when a lower air sweep gas flow rate is utilized.

The solution and electrochemical cell of this example was also tested over a period of 20 hours at a constant current of 6 mA and an air sweep gas rate of 0.05 L/min. The solution was circulated between the NO generating system and the fiber bundle continuously over the 20 hour time period. These results are shown in FIG. 11. As illustrated, in FIG. 11, a relatively constant level of NO was generated and extracted over the entire time period tested.

Overall, Example 6 illustrates that the fluid recirculation system disclosed herein can utilize an oxygen-containing gas as a sweep gas to pick up electrochemically generated NO and to generate an output gas stream. This example also illustrates that the NO generating system can reuse the solution to continuously generate desirable levels of NO, even if oxygen is introduced into the recirculated solution. Since there is no direct air purging into the solution, any O<sub>2</sub> in the solution should be dissolved O<sub>2</sub> from the air sweep gas (i.e., about 10 ppm at 100% saturation). This level will not reduce the NO production significantly.

#### Example 7

An aqueous solution was prepared with 7 mM Cu(II) Me<sub>3</sub>TACN, 1 M sodium nitrite and 0.5 M HEPES buffer (the solution was buffered to pH 7.3). The working electrode was a 4.5×4.5 cm<sup>2</sup> stainless steel mesh, and the reference/counter electrode was a 4.5×4.5 cm<sup>2</sup> stainless steel mesh. The generation of NO and the modulation of NO generation were performed by continuously adjusting the voltage to apply constant currents of 0 mA, 5 mA, 10 mA, and 20 mA for different time periods.

The solution containing the generated NO was pumped into a fiber bundle, where NO diffused through the fibers and excess solution was recirculated back into the container used for NO generation. Air was introduced into the fiber bundle as the sweep gas at a rate of 0.05 L/min. The resulting gas phase (containing air and NO) for each example at various currents was analyzed for NO content using chemiluminescence. The results are shown in FIG. 12. As depicted in FIG. 12, higher levels of NO were generated when the current was increased.

The solution and electrochemical cell of this example was also tested over a period of 24 hours at a constant current of 20 mA and an air sweep gas rate of 0.05 L/min. The solution was circulated between the NO generating system and the fiber bundle continuously over the 24 hour time period. These results are shown in FIG. 13. As illustrated, in FIG. 13, a relatively constant level of NO was generated and extracted over the entire time period tested.

Overall, Example 7 illustrates that the fluid recirculation system disclosed herein can utilize an oxygen-containing gas as a sweep gas to pick up NO generated by a stainless steel working electrode(s).

#### Example 8

An aqueous solution including from 2 mM to 7 mM Cu(II)Me<sub>3</sub>TACN and from 0.1 M to 1 M sodium nitrite was prepared. The aqueous solution was introduced into an electrolysis chamber including a working electrode (a 5×10 cm<sup>2</sup> gold mesh) and a reference/counter electrode (a 5×5 cm<sup>2</sup> platinum mesh). The generation of NO and the modulation of NO generation were performed by continuously adjusting the voltage to apply constant currents of 5 mA, 10 mA, 20 mA, and 30 mA for different time periods.

The solution containing the generated NO was pumped into a silicone hollow fiber-based gas separation module, where NO permeated the walls of the silicone fibers and excess solution was recirculated, via a micropump, back into the electrolysis chamber used for NO generation. Air was introduced into the silicone hollow fiber-based gas separation module as the sweep gas at rates of 0.1 L/min, or 0.2 L/min, or 0.05 L/min.

An electrochemical NO sensor was placed in the gas stream at the exit of the silicone hollow fiber-based gas separation module, and was used to detect the gas phase NO levels. As shown in FIG. 14A, the gas phase NO level in the air stream was controlled by the magnitude of the applied current to the working and counter electrodes and also by the flow rate of the air through the silicone hollow fiber-based gas separation module. Also as shown in FIG. 14A, when the air stream flow rate is slowed to only 0.05 L/min, higher levels of NO are able to accumulate in the air receiver stream, even when applied current is as little as 5 mA. If the air flow rate is slowed, the air collects higher amounts of NO from solution.

FIG. 14B depicts the calibration of the NO (ppm) versus varying levels of applied current at the 0.1 L/min air flow rate. This confirms that the gas phase NO level in the air stream was controlled, at least in part, by the magnitude of the applied current to the working and counter electrodes.

#### Example 9

An aqueous solution including from 2 mM to 7 mM Cu(II)Me<sub>3</sub>TACN and from 0.1 M to 1 M sodium nitrite was prepared. The aqueous solution was introduced into an electrolysis chamber including a working electrode (a 5×10 cm<sup>2</sup> gold mesh) and a reference/counter electrode (a 5×5 cm<sup>2</sup> platinum mesh). The generation of NO and the modulation of NO generation were performed by continuously adjusting the voltage to apply constant currents of 40 mA and 50 mA for different time periods.

The solution containing the generated NO was pumped into a silicone hollow fiber-based gas separation module, where NO permeated the walls of the silicone fibers and excess solution was recirculated, via a micropump, back into the electrolysis chamber used for NO generation. Air was introduced into the silicone hollow fiber-based gas separation module as the sweep gas.

The resulting gas phase (containing air and NO) for each example at the various currents was analyzed for NO content



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using chemiluminescence. The results are shown in FIG. 15. More specifically, the levels of NO, NO<sub>2</sub>, and total NO<sub>x</sub> in the outlet stream are depicted. As shown in FIG. 15, at applied current that enabled from about 50 ppm to about 60 ppm of NO in the recipient air stream, the amount of NO<sub>2</sub> present was less than 2% of the NO level. This NO<sub>2</sub> was likely from a reaction with oxygen in the recipient air stream, rather than having been generated by the electrochemical generation process.

FIG. 15 also shows a test bag of NO at 43 ppm with air in the bag. The results for the test bag show increased NO<sub>2</sub> levels, which were likely due to the longer exposure time in the presence of oxygen.

#### Example 10

The aqueous solution, electrolysis chamber, and silicone hollow fiber-based gas separation module described in Example 8 were used in this Example. An electrochemical NO/NO<sub>2</sub> sensor was placed in the gas stream (flow rate 1.0 L/min) at the exit of the silicone hollow fiber-based gas separation module. This sensor was electrically connected to electronic circuitry, which was used for feedback control. FIG. 16 illustrates a schematic diagram of the electronic circuitry used. The feedback from the electronic circuitry was used to control the applied current to the large area electrodes in contact with the circulating nitrite/Cu(II)-ligand solution based on signals from the sensor. As shown in FIG. 17, the feedback control approach can be employed to achieve stable NO gas phase levels with response times to targeted steady-state gas phase levels in less than 5 minutes at the 50 ppm and 100 ppm NO settings. In this example, silica gel was used to efficiently scavenge any low levels of NO<sub>2</sub>.

For a cardiopulmonary bypass application, the output gas stream may be merged with a stream of high oxygen content into a blood oxygenator, and a fraction of this merged stream may be pulled back over the NO/NO<sub>2</sub> sensor, so that levels of NO and NO<sub>2</sub> actually going into the oxygenator can be monitored and controlled.

#### Example 11

In this example, the CD11B expression by granulocytes and monocytes was tested over time during a simulated cardiopulmonary bypass (CPB) model. This simulation used a porcine model, and the animals were placed on extracorporeal circulation (ECC) for 2 hours. For control samples, no air blood interface (ABI) was used. For a comparative example, no nitric oxide (NO) was passed through the sweep gas side of the oxygenator (shown as “ABI” in FIGS. 18A and 18B). For other examples, NO was passed through the sweep gas side of the oxygenator (shown as “ABI+500 ppm NO sweep” and “ABI+50 ppm NO sweep” in FIGS. 18A and 18B). The NO was generated as described in Example 8. This output stream of NO and air was merged with a 100% oxygen stream at a 1:2 flow ratio, and the NO levels were continuously sensed in this stream with an NO gas sensor. CD11B expression was measured at baseline (BL), after 60 minutes (1 hour) of CPB, after 120 minutes (2 hours) of CPB, at 6 hours post CPB, and at 24 hours post CPB.

FIGS. 18A and 18B show the effectiveness of gaseous NO to reduce systemic inflammatory response syndrome (SIRS). CPB with air exposure (sample “ABI”) caused a large increase in CD11B expression by both granulocytes (FIG. 18A) and monocytes (FIG. 18B) in this model. When a high dose of 500 ppm NO was added to the sweep gas (sample

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“ABI+500 ppm NO sweep”), the expression of CD11B on granulocytes (FIG. 18A) and monocytes (FIG. 18B) was maintained within the normal range (see the control sample). Lower doses of NO were also quite effective, as shown in FIGS. 18A and 18B when using a dose of 50 ppm NO. Even at 500 ppm NO, there was minimal change in met-Hb levels after 2 hours (less than 3%). These results demonstrate the significant protective effects of NO on white blood cell (WBC) activation.

It is to be understood that the ranges provided herein include the stated range and any value or sub-range within the stated range, as if the value(s) or sub-range(s) within the stated range were explicitly recited. For example, a range from about 100 ppbv to about 100 ppmv should be interpreted to include not only the explicitly recited limits of about 100 ppbv to about 100 ppmv, but also to include individual values, such as 150 ppbv, 50.5 ppmv, 75 ppmv, etc., and sub-ranges, such as from about 300 ppbv to about 30 ppmv, etc.

Furthermore, when “about” is utilized to describe a value, this is meant to encompass minor variations (up to +/-10%) from the stated value. When applied potential values are discussed, it is to be understood that wider ranges may be suitable. In some of the examples disclosed herein, increasing the magnitude of the cathodic potential pulse (i.e., a more negative cathodic potential) increases the amount of Cu(I)-ligand complex that is generated, and thus also increases the amount of NO generated. As such, it is believed that a broad range is applicable for the applied potential values, the limits of which may depend on the desired amount of Cu(I) species and NO to be generated.

Furthermore, reference throughout the specification to “one example”, “another example”, “an example”, and so forth, means that a particular element (e.g., feature, structure, and/or characteristic) described in connection with the example is included in at least one example described herein, and may or may not be present in other examples. In addition, it is to be understood that the described elements for any example may be combined in any suitable manner in the various examples unless the context clearly dictates otherwise.

While several examples have been described in detail, it is to be understood that the disclosed examples may be modified. Therefore, the foregoing description is to be considered non-limiting.

What is claimed is:

1. A gas delivery device, comprising:
  - a nitric oxide generating system, including:
    - a medium including a source of nitrite ions;
    - a working electrode in contact with the medium;
    - a Cu(II)-ligand complex in contact with the working electrode; and
    - one of: a reference/counter electrode or a reference electrode and a counter electrode in contact with the medium and separated from the working electrode;
  - an inlet conduit to deliver nitrogen gas to the medium;
  - an outlet conduit to transport a stream of nitrogen gas and nitric oxide from the medium;
  - an inspiratory gas conduit operatively connected to the outlet conduit to introduce an oxygen-containing gas and form an output gas stream of the gas delivery device;
  - a sensor in contact with the output gas stream to monitor a nitric oxide level of the output gas stream; and
  - electronic circuitry electrically connected to the sensor and to the nitric oxide generating system to provide



feedback control to the nitric oxide generating system based on signals from the sensor.

2. The gas delivery device as defined in claim 1, further comprising:

a separator operatively positioned between the outlet conduit and the inspiratory gas conduit, the separator including:

a housing containing a nitric oxide permeable material separating two spaces;

a first housing inlet operatively connected to the outlet conduit to receive, in a first of the two spaces, the stream of nitrogen gas and nitric oxide from the outlet conduit;

a second housing inlet operatively connected to the inspiratory gas conduit to receive, in a second of the two spaces, the oxygen-containing gas, which mixes with nitric oxide diffusing through the nitric oxide permeable material to form the output gas stream; and

a housing output conduit to transport the output gas stream to a recipient.

3. The gas delivery device as defined in claim 2 wherein the nitric oxide permeable material is selected from the group consisting of a membrane and a hollow fiber bundle.

4. The gas delivery device as defined in claim 2, further comprising an inhalation unit operatively connected to the housing output conduit.

5. The gas delivery device as defined in claim 2, further comprising an oxygenator operatively connected to the housing output conduit.

6. The gas delivery device as defined in claim 1, further comprising:

a delivery conduit operatively connected to the outlet conduit and the inspiratory gas conduit; and

an inhalation unit operatively connected to the delivery conduit.

7. The gas delivery device as defined in claim 1 wherein: the Cu(II)-ligand complex is selected from the group consisting of Cu(II)-tri(2-pyridylmethyl)amine, Cu(II)-tri(2-dimethylamino)ethylamine, Cu(II)-tri(2-pyridylmethyl)phosphine, Cu(II)-1,4,7-trimethyl-1,4,7-triazacyclononane,

Cu(II)-1,4,7-triethyl-1,4,7-triazacyclononane,

Cu(II)-1,4,7-tripropyl-1,4,7-triazacyclononane,

Cu(II)-1,4,7-triisopropyl-1,4,7-triazacyclononane,

Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-ethylate),

Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-propanoate),

Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-butylate),

Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-ethylate),

Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-propanoate),

Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-butylate),

Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-methyl-phenolate),

Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-ethyl-phenolate),

Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-propyl-phenolate),

Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-methyl-phenolate),

Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-ethyl-phenolate),

Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-propyl-phenolate),

Cu(II)-3-((2-(pyridin-2-yl)ethyl)(pyridin-2-ylmethyl)amino)ethylate,

Cu(II)-3-((2-(pyridin-2-yl)ethyl)(pyridin-2-ylmethyl)amino)propanoate,

Cu(II)-3-((2-(pyridin-2-yl)ethyl)(pyridin-2-ylmethyl)amino)butylate,

Cu(II)-2-(pyridin-2-yl)-N,N-bis(pyridin-2-ylmethyl)ethan-1-amine,

Cu(II)-2,2'-(2-(2-(pyridin-2-yl)ethyl)butane-1,4-diyl)dipyridine, and combinations thereof; and

the source of nitrite ions is any water soluble, inorganic or organic nitrite salt.

8. The gas delivery device as defined in claim 1 wherein the working electrode is selected from the group consisting of platinum, gold, carbon, a carbon coated material, mercury, stainless steel, a base electron conducting material having a thin film of platinum thereon, and a base electron conducting material having a thin film of gold thereon.

9. The gas delivery device as defined in claim 1, further comprising:

an oxygen scrubber operatively connected to the inlet conduit; and

a pump operatively connected to the oxygen scrubber, the pump to introduce ambient air into the oxygen scrubber.

10. The gas delivery device as defined in claim 9 wherein the oxygen scrubber includes a solution or a particle bed to at least partially remove oxygen from the ambient air to generate a nitrogen purge gas stream including the nitrogen gas.

11. The gas delivery device as defined in claim 1 wherein the Cu(II)-ligand complex is dissolved or dispersed in the medium.

12. The gas delivery device as defined in claim 1 wherein the Cu(II)-ligand complex is immobilized on a surface of the working electrode.

13. A gas delivery device, comprising:

a nitric oxide generating system, including:

a first housing;

a medium contained in the first housing, the medium including a source of nitrite ions;

a working electrode in contact with the medium;

a Cu(II)-ligand complex in contact with the working electrode; and

one of: a reference/counter electrode or a reference electrode and a counter electrode in contact with the medium and separated from the working electrode;

a nitric oxide extraction device, including:

a second housing;

a nitric oxide permeable medium positioned in the second housing;

a space at least partially surrounding the nitric oxide permeable medium, the space including an input area to receive a nitric-oxide containing solution from the nitric oxide generating system and an output area to transport an at least substantially reduced nitric-oxide solution out of the nitric oxide extraction device;

an inlet conduit to deliver a sweep gas to the nitric oxide permeable medium, the sweep gas being selected from the group consisting of nitrogen gas, an oxygen-containing gas, and combinations thereof; and

an outlet conduit to transport a mixed gas stream from the nitric oxide permeable medium, the mixed gas stream including the nitric oxide and the sweep gas;

a fluid recirculation system fluidly connecting the first housing and the second housing;

a delivery conduit operatively connected to the outlet conduit;

a nitric oxide sensor positioned in the delivery conduit or another conduit split off of the delivery conduit; and

electronic circuitry electrically connected to the sensor and to the nitric oxide generating system to provide feedback control to the nitric oxide generating system based on signals from the sensor.

14. The gas delivery device as defined in claim 13 wherein the sweep gas is the nitrogen gas, and wherein the gas delivery device further comprises an inspiratory gas conduit



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operatively connected with the outlet conduit to introduce an oxygen-containing gas to the mixed gas stream to form an output gas stream.

15. The gas delivery device as defined in claim 14, wherein:

the delivery conduit is also operatively connected to the inspiratory gas conduit; and

the gas delivery device further comprises an inhalation unit operatively connected to the delivery conduit.

16. The gas delivery device as defined in claim 13 wherein the fluid recirculation system includes:

a first conduit connecting an outlet of the first housing to an inlet of the second housing;

a second conduit connecting an outlet of the second housing to an inlet of the first housing; and

a pump to transport the nitric-oxide containing solution through the first conduit into the nitric oxide extraction device and to transport the at least substantially reduced nitric-oxide solution through the second conduit into the nitric oxide generating system.

17. The gas delivery device as defined in claim 13, further comprising an oxygenator operatively connected to the outlet conduit.

18. The gas delivery device as defined in claim 13 wherein:

the Cu(II)-ligand complex is selected from the group consisting of Cu(II)-tri(2-pyridylmethyl)amine, Cu(II)-tri(2-dimethylamino)ethylamine, Cu(II)-tri(2-pyridylmethyl)phosphine, Cu(II)-1,4,7-trimethyl-1,4,7-triazacyclononane, Cu(II)-1,4,7-triethyl-1,4,7-triazacyclononane, Cu(II)-1,4,7-tripropyl-1,4,7-triazacyclononane, Cu(II)-1,4,7-triisopropyl-1,4,7-triazacyclononane, Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-ethylate), Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-propanoate), Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-butylate), Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-ethylate), Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-propanoate), Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-butylate), Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-methyl-phenolate), Cu(II)-(N,

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N-bis-(2-pyridylmethyl)amine-N-ethyl-phenolate), Cu(II)-(N,N-bis-(2-pyridylmethyl)amine-N-propyl-phenolate), Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-methyl-phenolate), Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-ethyl-phenolate), Cu(II)-(N,N-bis-(2-pyridylethyl)amine-N-propyl-phenolate), Cu(II)-3-((2-(pyridin-2-yl)ethyl)(pyridin-2-ylmethyl)amino)ethylate, Cu(II)-3-((2-(pyridin-2-yl)ethyl)(pyridin-2-ylmethyl)amino)propanoate, Cu(II)-3-((2-(pyridin-2-yl)ethyl)(pyridin-2-ylmethyl)amino)butylate, Cu(II)-2-(pyridin-2-yl)-N,N-bis(pyridin-2-ylmethyl)ethan-1-amine, Cu(II)-2,2'-(2-(2-(pyridin-2-yl)ethyl)butane-1,4-diyl)dipyridine, and combinations thereof; and

the source of nitrite ions is any water soluble, inorganic or organic nitrite salt.

19. The gas delivery device as defined in claim 13 wherein the working electrode is selected from the group consisting of platinum, gold, carbon, a carbon coated material, mercury, a base electron conducting material having a thin film of platinum thereon, and a base electron conducting material having a thin film of gold thereon.

20. The gas delivery device as defined in claim 13 wherein the sweep gas is the nitrogen gas, and wherein the gas delivery device further comprises:

an oxygen scrubber operatively connected to the inlet conduit; and

a pump operatively connected to the oxygen scrubber, the pump to introduce ambient air into the oxygen scrubber.

21. The gas delivery device as defined in claim 20 wherein the oxygen scrubber includes a solution or a particle bed to at least partially remove oxygen from the ambient air to generate a nitrogen purge gas including the nitrogen gas.

22. The gas delivery device as defined in claim 13 wherein the Cu(II)-ligand complex is dissolved or dispersed in the medium.

23. The gas delivery device as defined in claim 13 wherein the Cu(II)-ligand complex is immobilized on a surface of the working electrode.

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